The American Journal of Medicine

Vol. XXIX NOVEMBER 1960 No. 5

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Clinical Studies

Fatal Complications of Virus Hepatitis in Two Patients with Agammaglobulinemia
Robert A. Good and Arthur R. Page 804

In two patients with agammaglobulinemia, acquired in one instance and congenital in the other, jaundice (presumably homologous serum hepatitis) developed which rapidly progressed to hepatic insufficiency and death. The authors make the interesting point that if, as has been suggested, chronic hepatitis and postnecrotic cirrhosis really do represent autoimmune disease of the liver, how explain the fulminating development of these complications of virus hepatitis in these two agammaglobulinemic patients who presumably were incapable of the postulated immune response? Obviously re-examination of the assumptions underlying the hypothesis of autoimmune disease of the liver is in order.

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VOLUME TWENTY-NINE NUMBER FIVE

Hereditary Non-Spherocytic Hemolytic Disease
CAPT. MARCEL E. CONRAD, JR., COL. WILLIAM H. CROSBY AND LT. COL. DONALD L. HOWIE 811

Despite recent clarification of the pathogenesis of certain syndromes characterized by high plasma levels of unconjugated bilirubin, there is still much confusion in the classification of these syndromes. One of them, often overlooked or misclassified, is hereditary non-spherocytic hemolytic disease, here described on the basis of an experience with twenty cases. This is a familial form of intracorpuscular defect leading to more or less hemolysis, but unassociated with distinctive morphologic or as yet recognized biochemical defects. As the authors point out, there can be little doubt that some cases have heretofore been classified as constitutional hepatic dysfunction (Gilbert's disease) which can, however, be ruled out by red cell survival studies.

Familial Hyperoxaluria. Report of a Family Review of the Literature
RICHARD A. DANIELS, ROBERT MICHELS, PHILIP AISEN AND GILBERT GOLDSTEIN 820

Hyperoxaluria was found to be the genesis of stone formation in several siblings—another example of familial hyperoxaluria. This condition, and what is known of the metabolic and/or renal tubular reabsorptive defect responsible for it, is discussed informatively.

Review

The Design and Analysis of Isotope Experiments . . . . . D. B. ZILVERSMIT 832

Isotope incorporation technics have become an exceedingly important part of the methodology of clinical investigation but, because of the complexity of metabolic interrelations, require utmost circumspection in experimental design and interpretation of results. Dr. Zilversmit illustrates this necessity by pointing up the problems in a variety of circumstances taken particularly from his own experience. After defining and explaining terms, in particular the meaning of "turnover," he considers the problems involved in interpretation of plasma disappearance curves, the specific activity of precursors when maintained constant and when changing linearly or exponentially, the difficulties introduced when (as commonly occurs) there are multiple precursors and the metabolic pools are inhomogeneous, and many related problems. Equations to give approximate numerical solutions in these various situations are considered.

Case Reports

Splenic Arteriovenous Fistulas as a Cause of Portal Hypertension
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An interesting case.

Cryoglobulinemia. Rationale of Treatment of a Case Based on Unusual Properties of the Cryoprotein
ROBERT D. KOLER, DEMETRIOS A. RIGAS, ARTHUR J. SEAMAN, BERNARD PIROFSKY AND ROY L. SWANK 857

A case of unusual interest.

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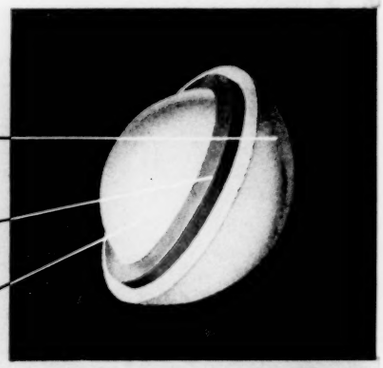
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VOLUME TWENTY-NINE NUMBER FIVE

Embolic Osteomyelitis of the Spine as a Complication of Infection of the Urinary Tract
MICHAEL S. BRUNO, THOMAS N. SILVERBERG AND DAVID H. GOLDSTEIN 865

An account of three cases of embolic osteomyelitis of the spine, with an informative review.

Fusobacterium Septicemia . . . . . BAYARD S. TYNES AND JOHN P. UTZ 879

A well studied case, with review of the literature.

Occurrence of Retinal Pigmentation, Ophthalmoplegia, Ataxia, Deafness and Heart Block. Report of a Case, with Findings at Autopsy
B. V. JAGER, HERBERT L. FRED, RONALD B. BUTLER AND WILLIAM H. CARNES 888

An example of Refsun's syndrome or a related disorder combining retinal pigmentation and ophthalmoplegia with a variety of abnormalities. Of special interest in this case was the early appearance of facial muscle weakness and external ophthalmoplegia simulating myasthenia gravis.

Systemic Mast Cell Disease. Physiologic Considerations and Report of a Patient Treated with Nitrogen Mustard
LEON STUTZMAN, STEPHAN ZSOLDOS, JULIAN L. AMBRUS AND G. ASBOE-HANSEN 894

A case of mastocytosis, with hepatosplenomegaly, associated with urticaria and pigmentosa.

Central Pontine Myelinolysis
ORVILLE T. BAILEY, MICHAEL S. BRUNO AND WILLIAM B. OBER 902

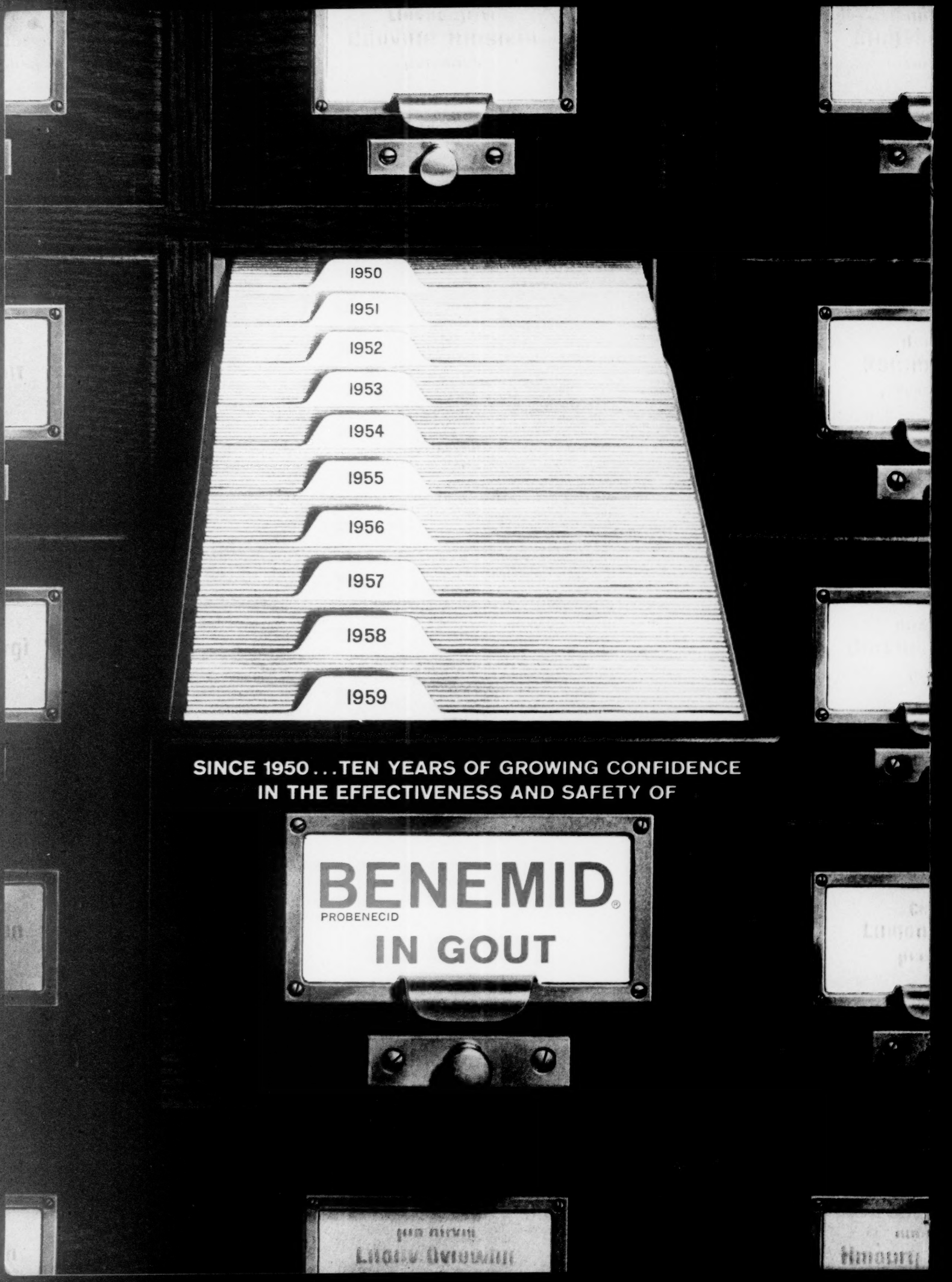
An instructive report of a newly recognized syndrome.

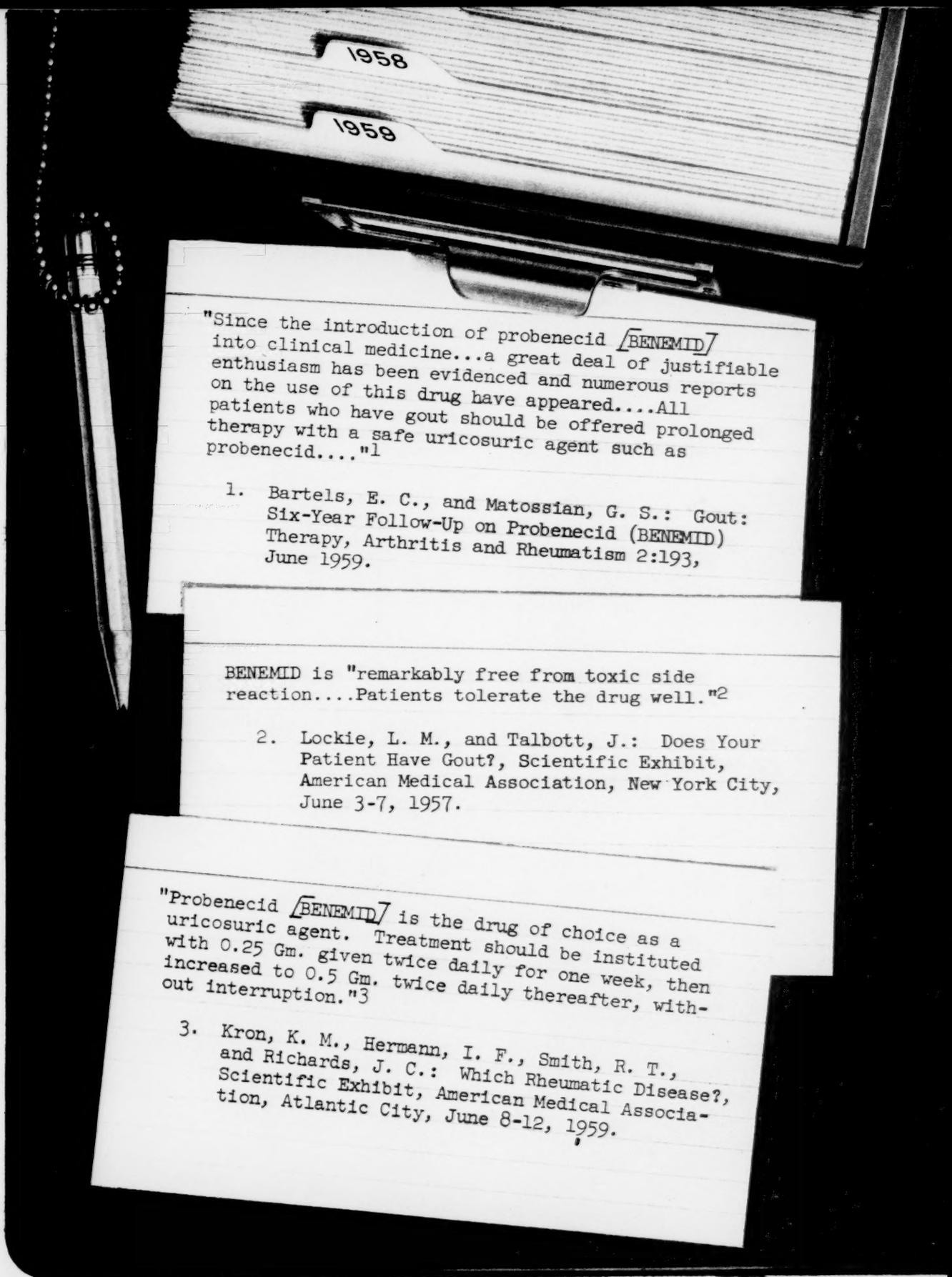
ERRATUM

Illustrations in the article "The Value of Splenic Portography in the Diagnosis of Intrahepatic and Extrahepatic Neoplasm" by Ruzicka et al., which appeared in the September issue, pages 434–443, were included through the courtesy of The New York Academy of Sciences (Fig. 1A. RUZICKA, F. F., JR., BRADLEY, E. G. and ROUSSELOT, L. M. Two-phase opacification of the liver in cirrhosis. *Ann. New York Acad. Sc.*, 78: 819, 1959), W. B. Saunders Co. (Fig. 2A. PANKE, W. F., MORENO, A. H. and ROUSSELOT, L. M. The place of surgery in cirrhosis of the liver. *Surg. Clin. North America*, p. 1293, 1958), Paul B. Hoeber, Inc. (Fig. 6A. RUZICKA, F. F., JR., DOEHNER, G. A. and ROUSSELOT, L. M. Portal venography. Anatomic and physiologic considerations in interpretation. *Am. J. Digest., Dis.*, 1: 1, 1956), the American Medical Association (Fig. 6B. PANKE, W. F., BRADLEY, E. G., MORENO, A. H., RUZICKA, F. F., JR. and ROUSSELOT, L. M. Technique, hazards and usefulness of percutaneous splenic portography. *J.A.M.A.*, 169: 1032, 1959) and the Radiological Society (Fig. 7B. RUZICKA, F. F., JR., BRADLEY, E. G. and ROUSSELOT, L. M. The intrahepatic vasculogram and hepatogram in cirrhosis following percutaneous splenic injection. *Radiology*, 71: 175, 1958).

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References: (1) Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959. (2) Modarress, Y.; Ryan, R. J., & Francis, Sr. C.: *J. M. Soc. New Jersey* 57:168, 1960. (3) Petersdorf, R. G., *et al.*: *Arch. Int. Med.* 105:398, 1960. (4) Rebhan, A. W., & Edwards, H. E.: *Canad. M.A.J.* 82:513, 1960. (5) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (6) Olarte, J., & de la Torre, J. A.: *Am. J. Trop. Med.* 8:324, 1959: (7) Berle, B. B., *et al.*: *New York J. Med.* 59:2383, 1959. (8) Fisher, M. W.: *Arch. Int. Med.* 105:413, 1960.

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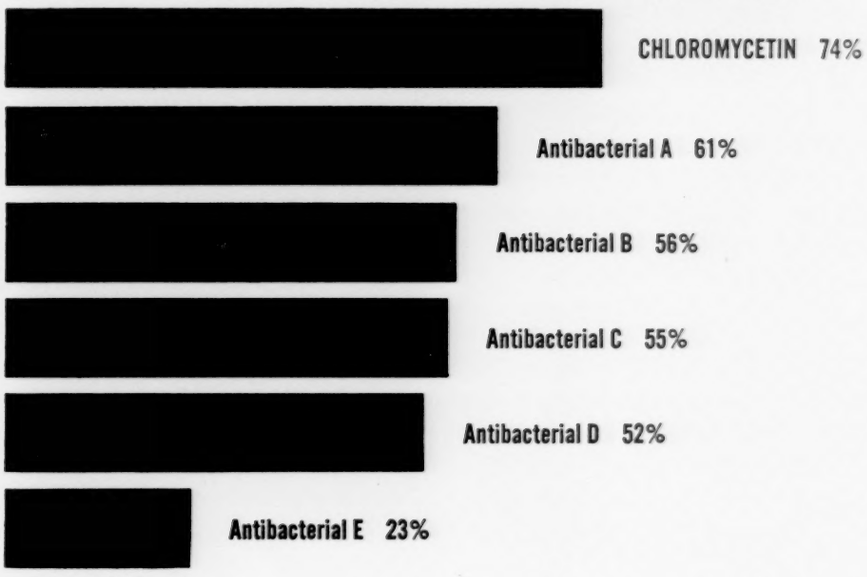
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References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

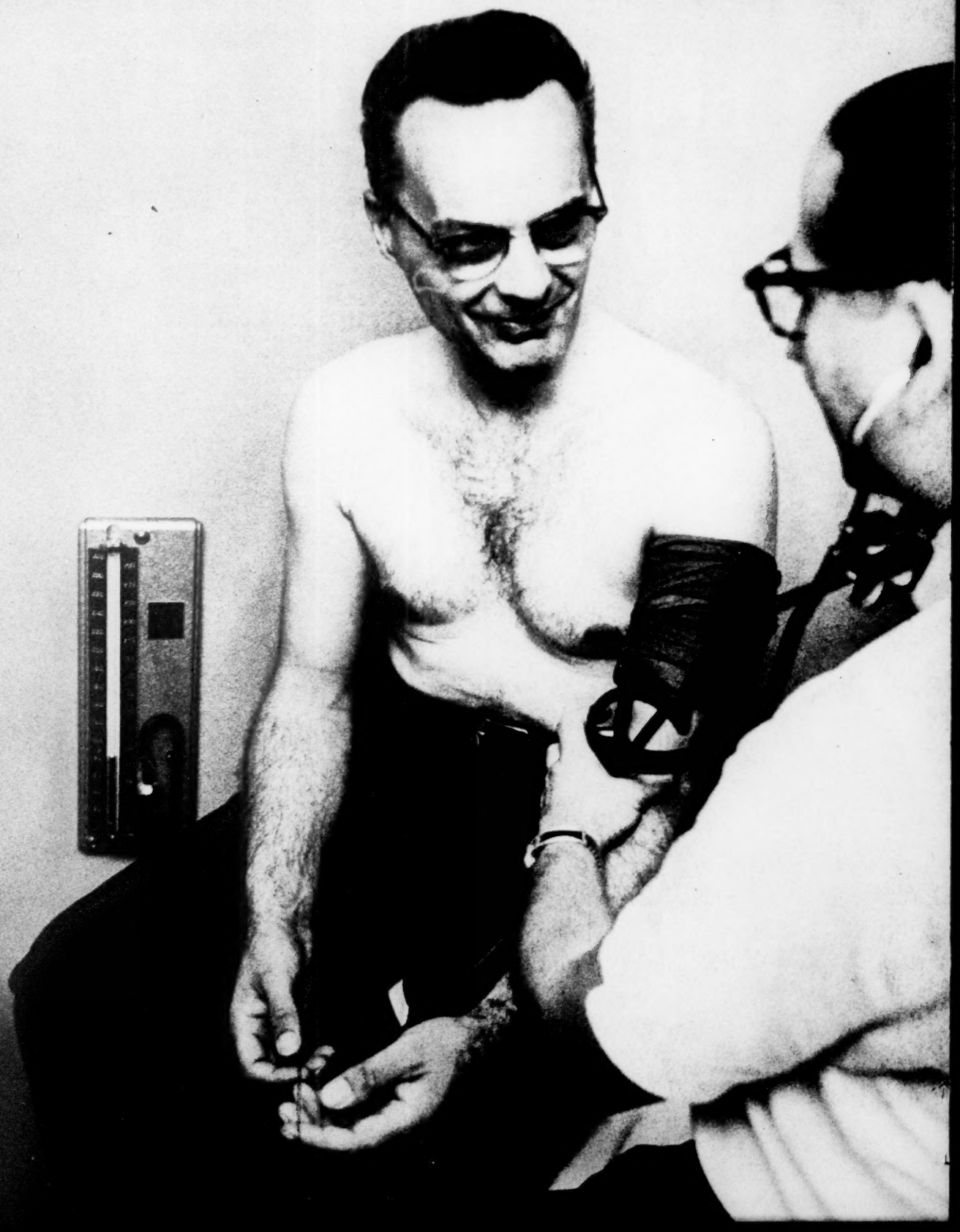
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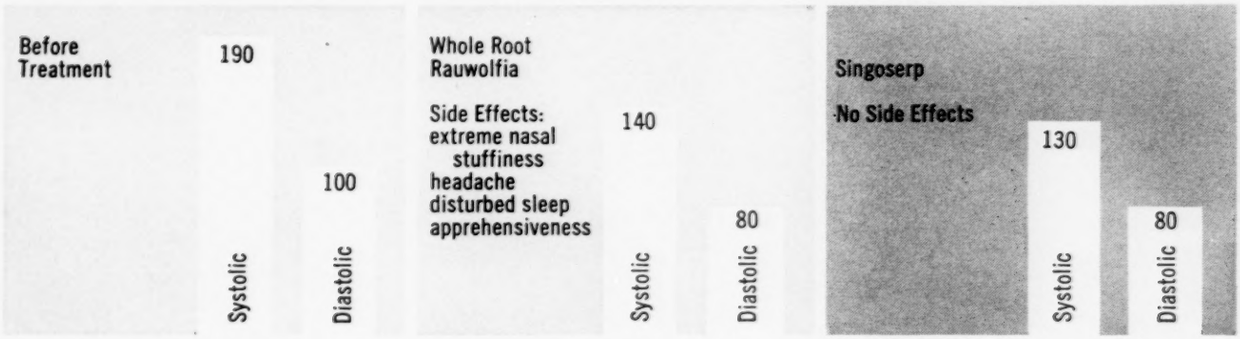
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1. Barr, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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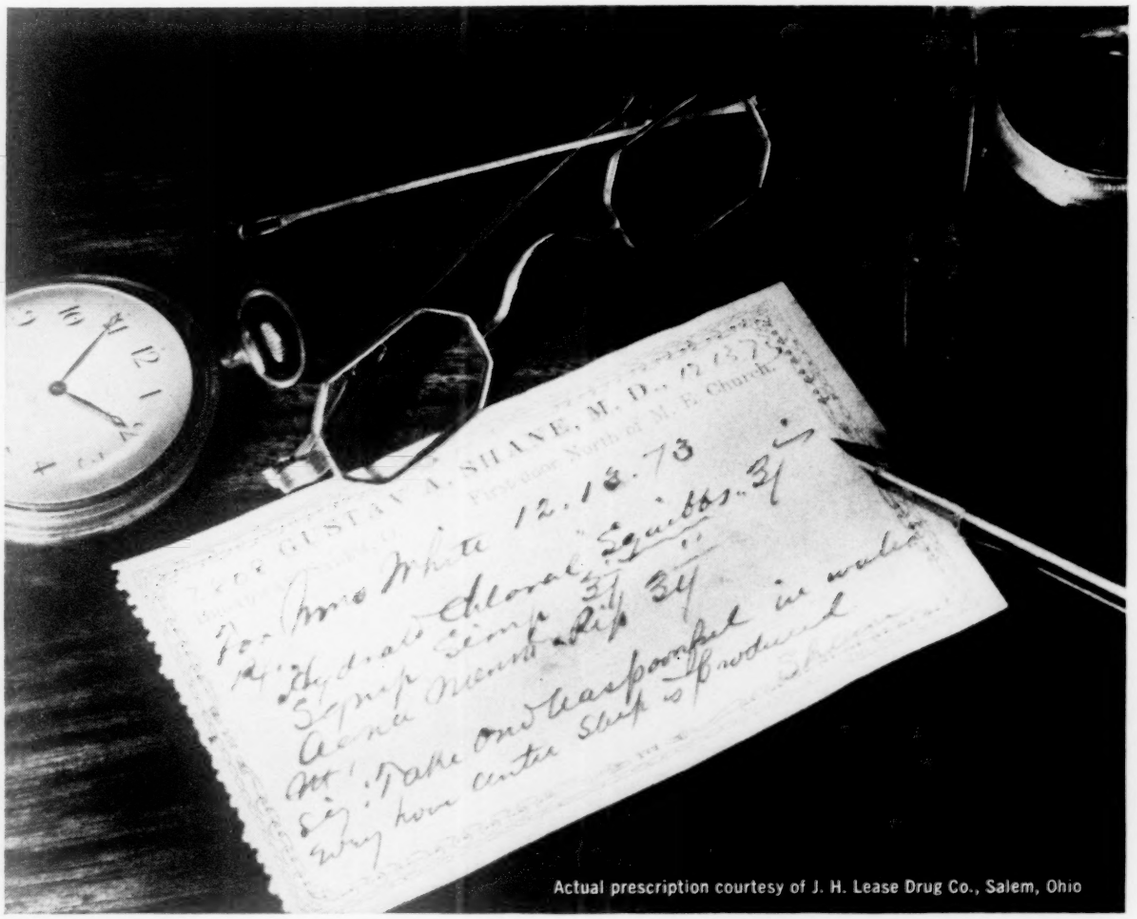
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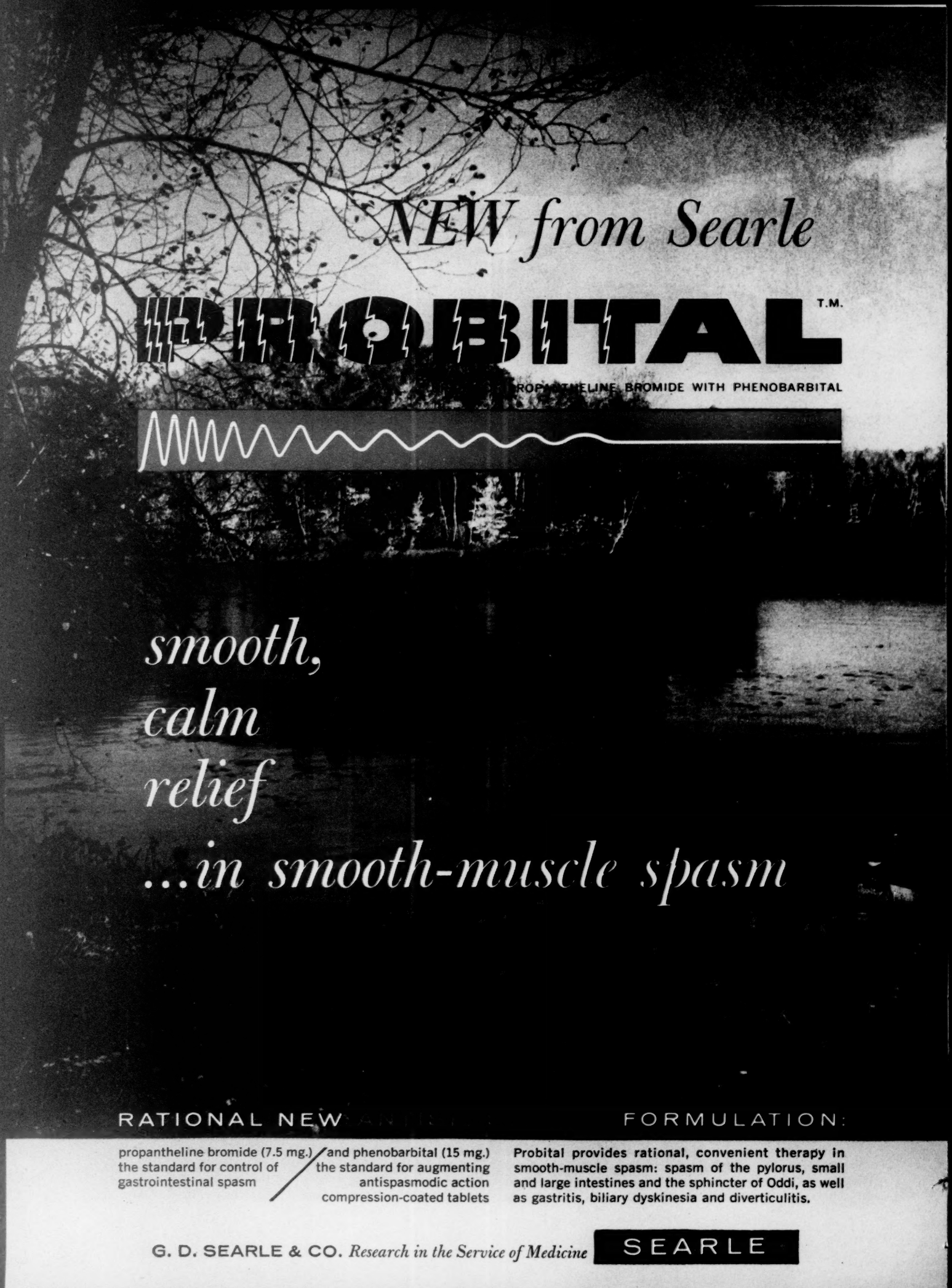
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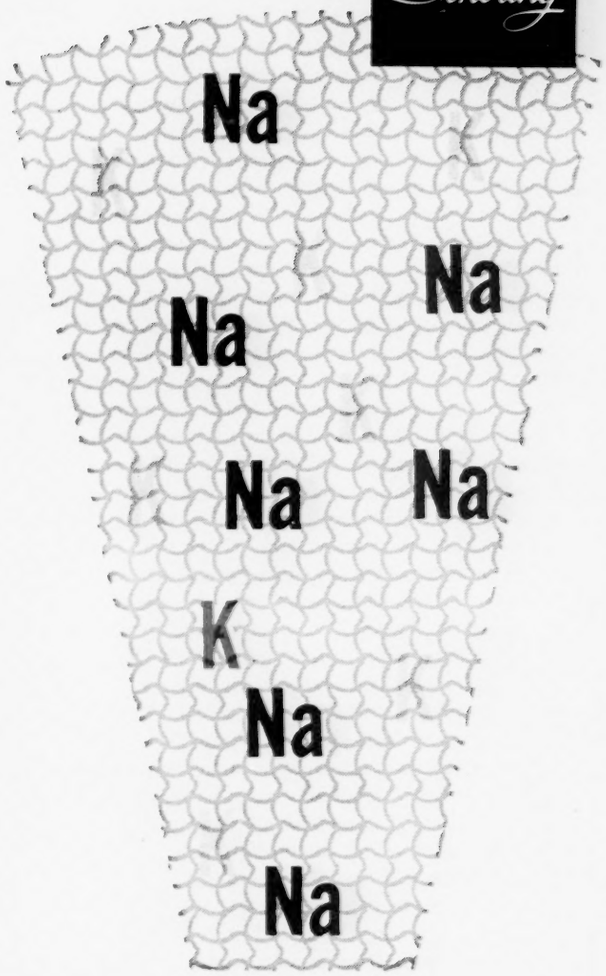
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Ammonium chloride	8 gr.
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Menthol	q.s.
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Supplied: Bottles of 16 ounces and 1 gallon.

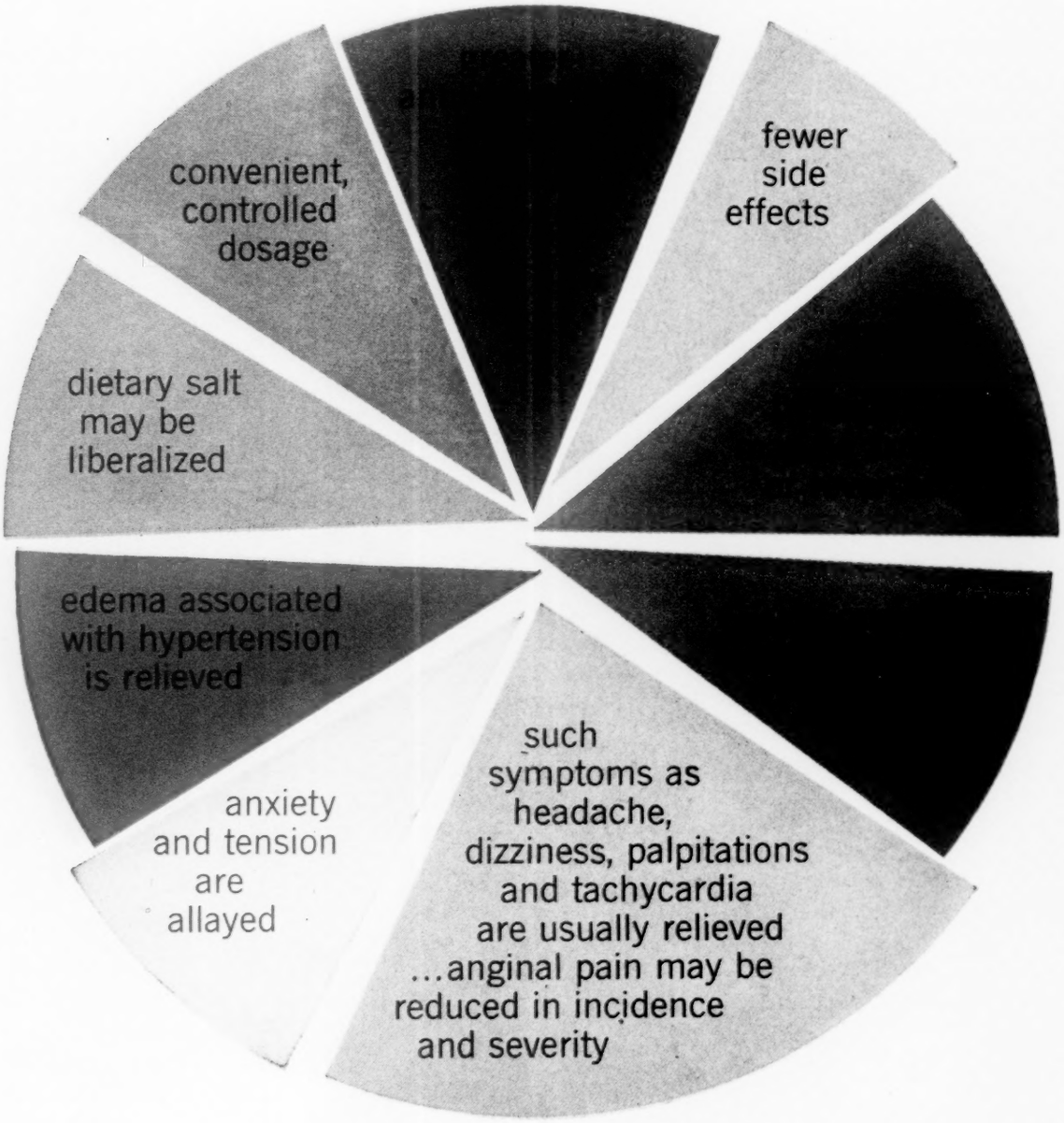
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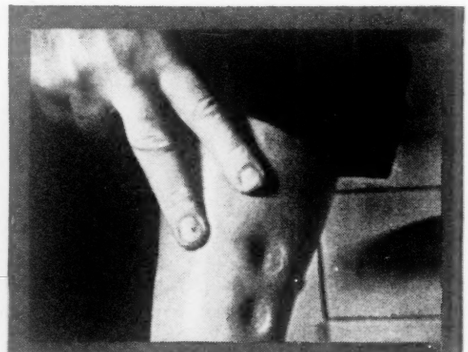
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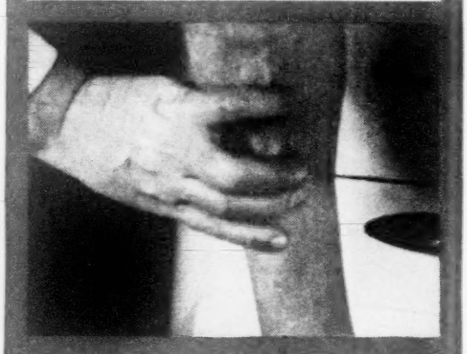
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with Esidrix, 12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

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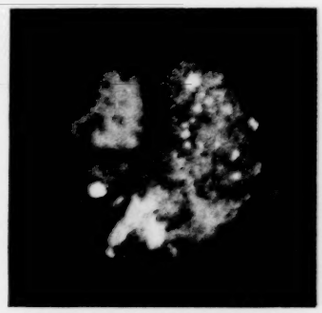
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Proctoscopic view of the sigmoid in acute stage of ulcerative colitis



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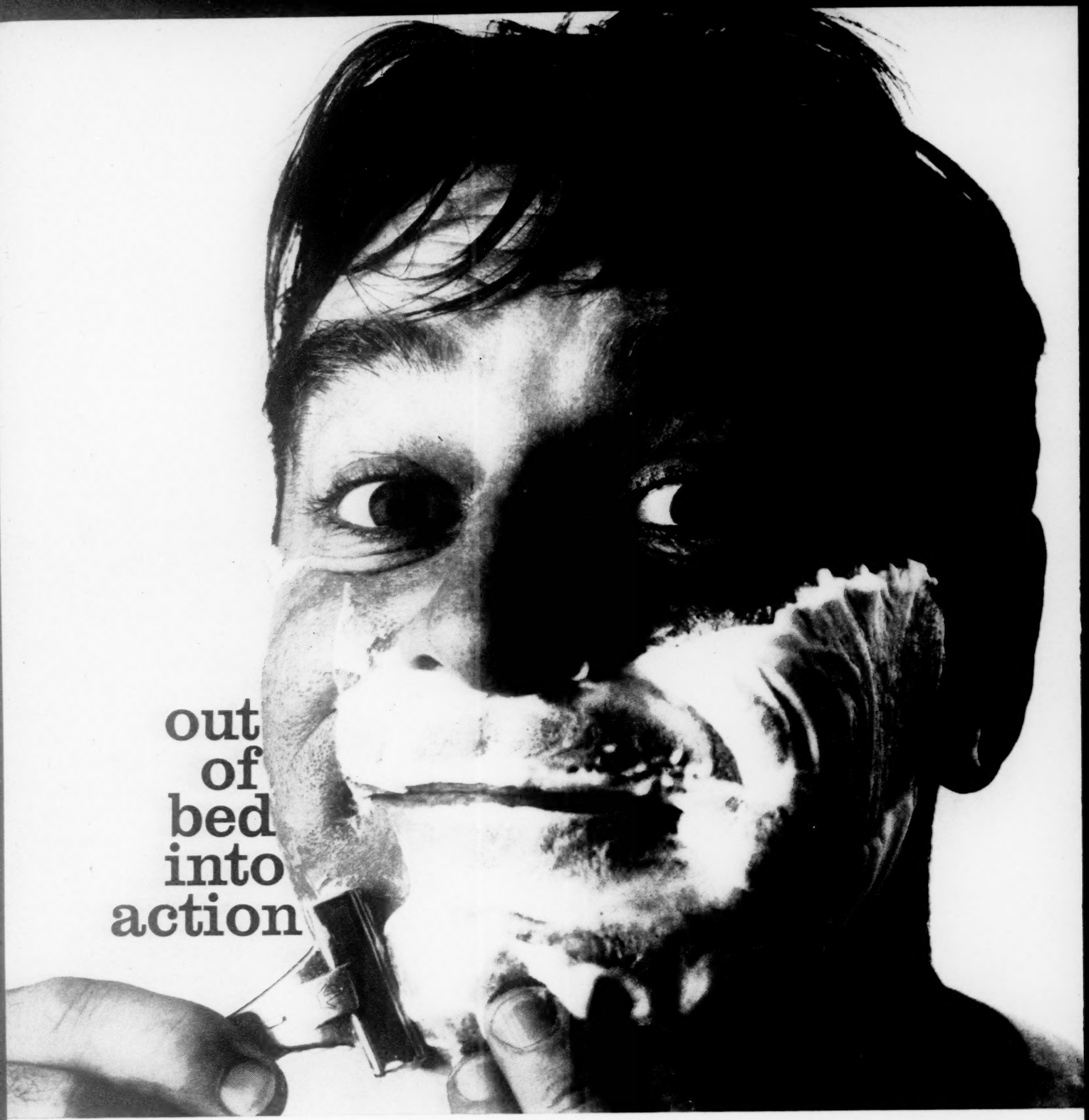
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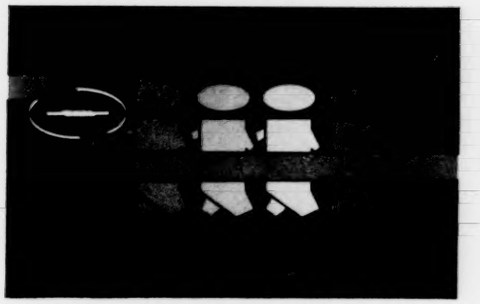
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INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

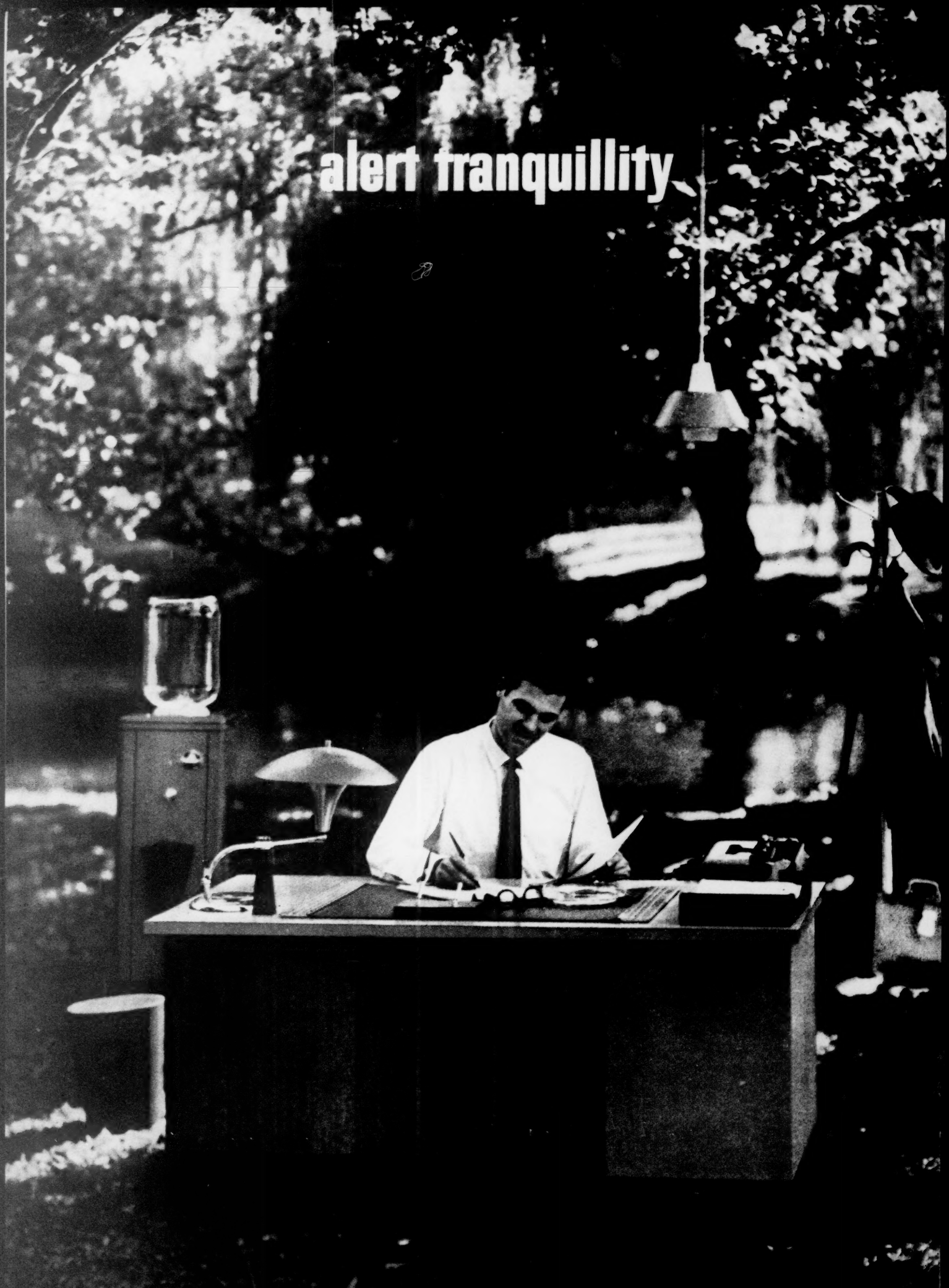
Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used: most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

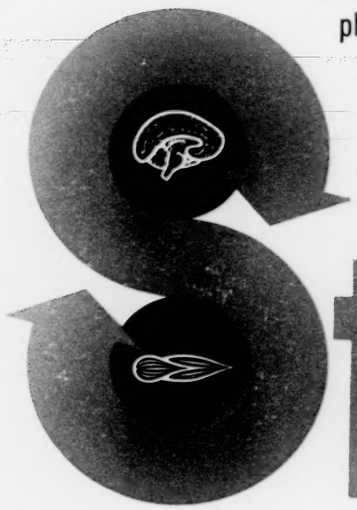
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alert tranquillity

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- no cumulative effect
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STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

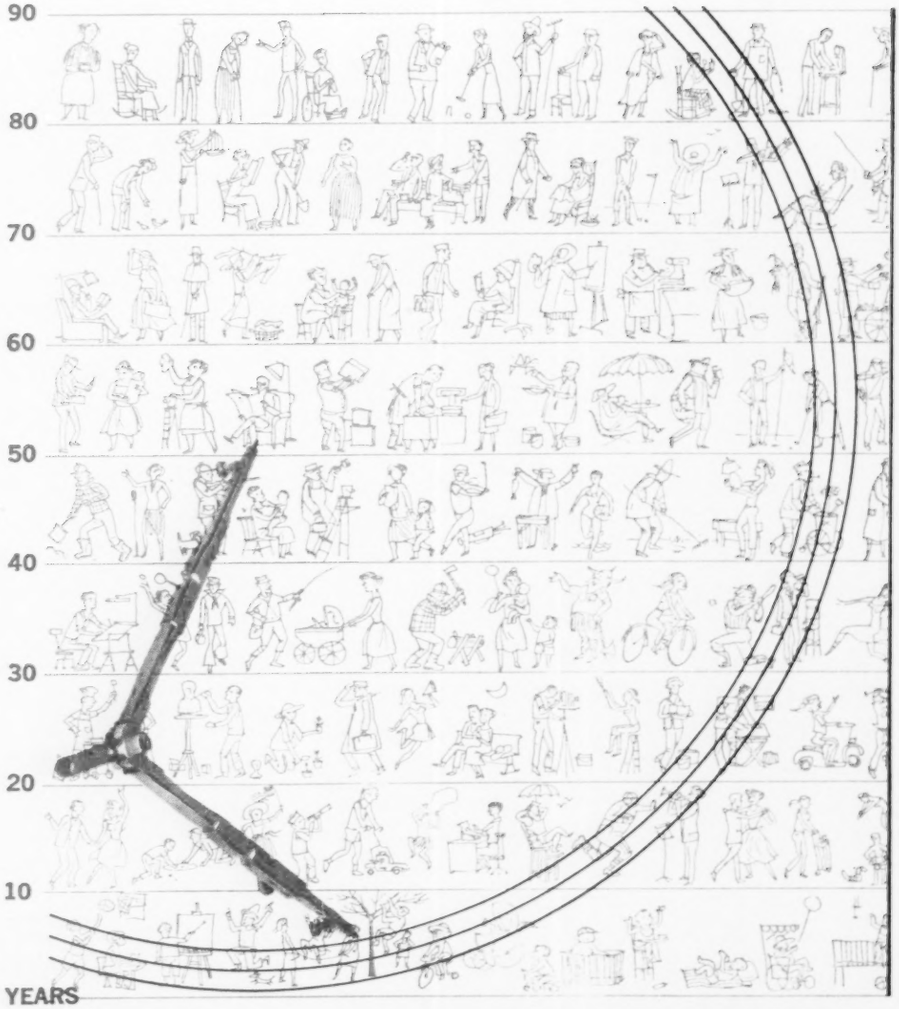
Supply: 200 mg. tablets, coated pink, bottles of 100.

While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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Complete bibliography available on request.

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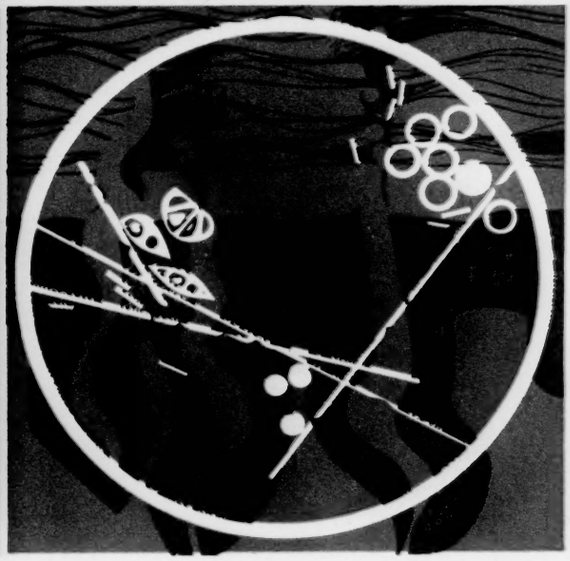
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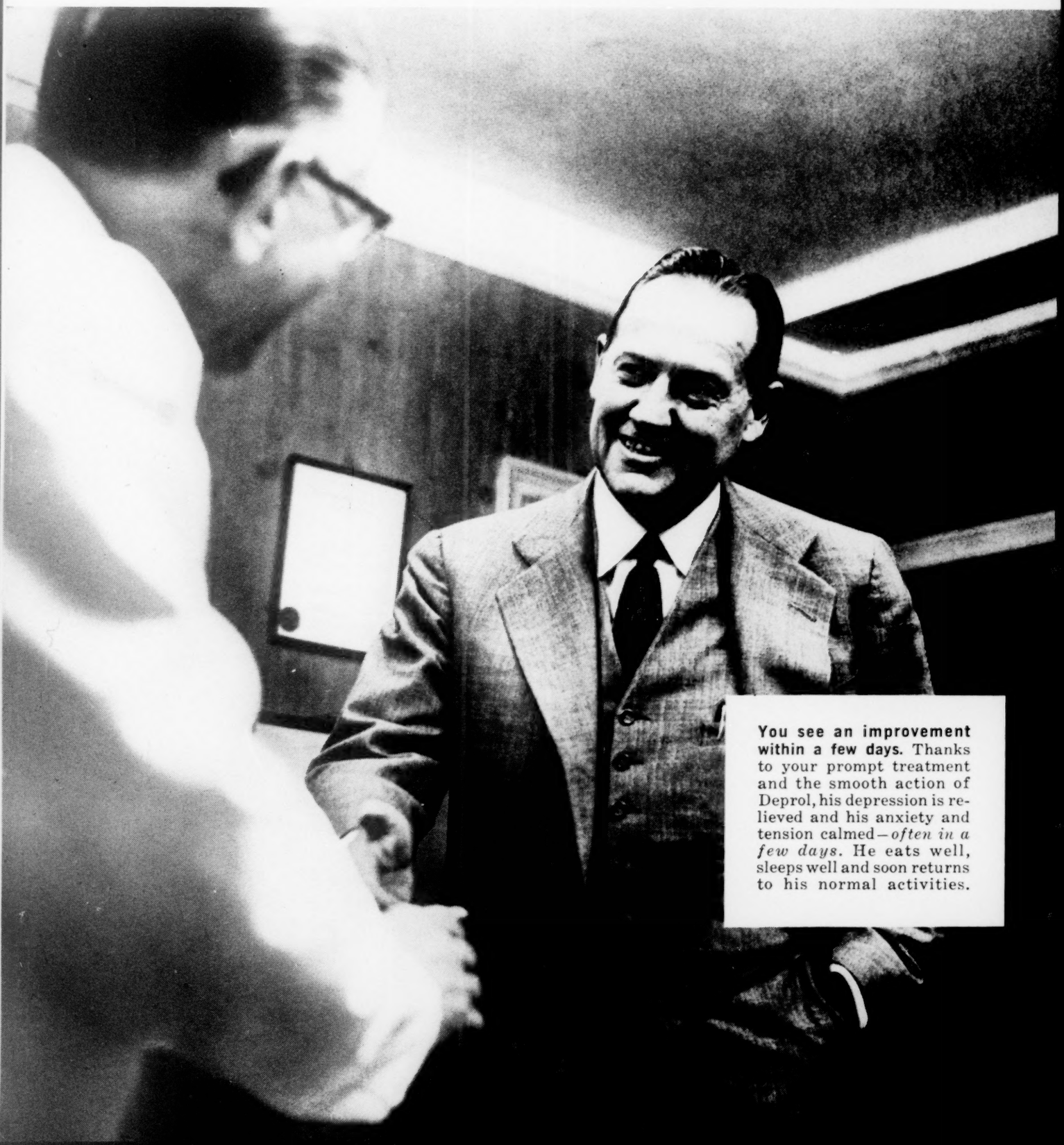
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Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other antidepressant drugs.

Bibliography *(13 clinical studies, 858 patients)*: **1.** Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

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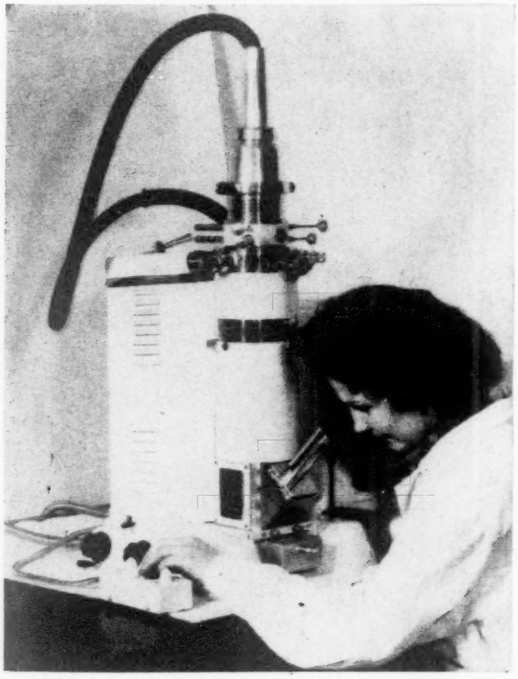
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Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

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1. Richardson, M. E.: J. Am. Osteop. A. 57:562 (May) 1958. 2. Mason, M. L.: Northwest Med. 57:1439 (Nov.) 1958. 3. Coleman, S. S.: Am. J. Surg. 97:43 (Jan.) 1959.

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References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

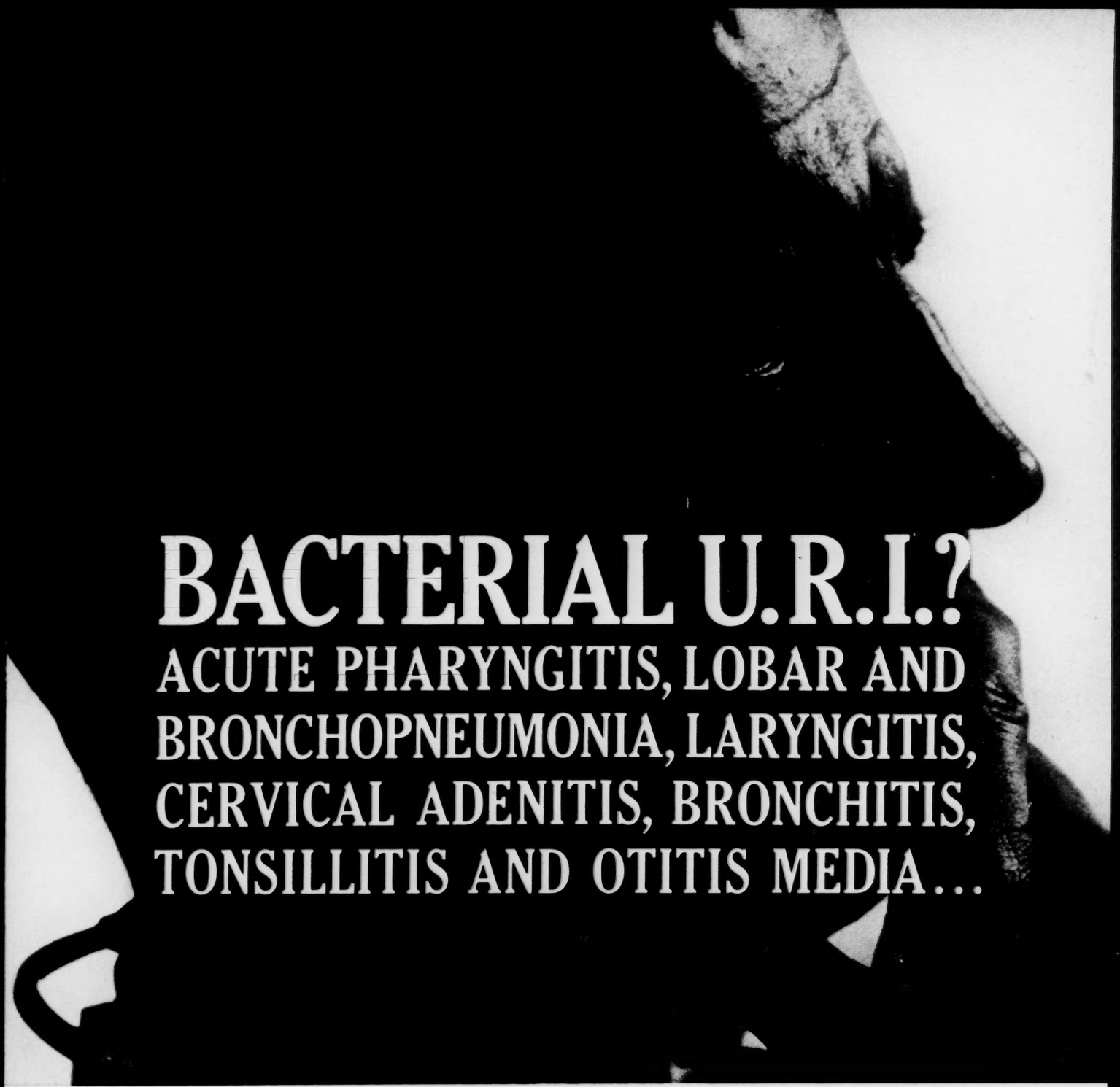
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1. Morigi, E. M. E.; Wheatley, W. B., and Albright, H.: Antibiotics Annual 1959-60, N.Y., Antibiotic, Inc., 1960, 131

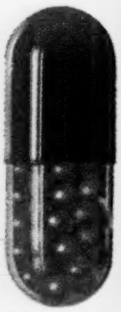
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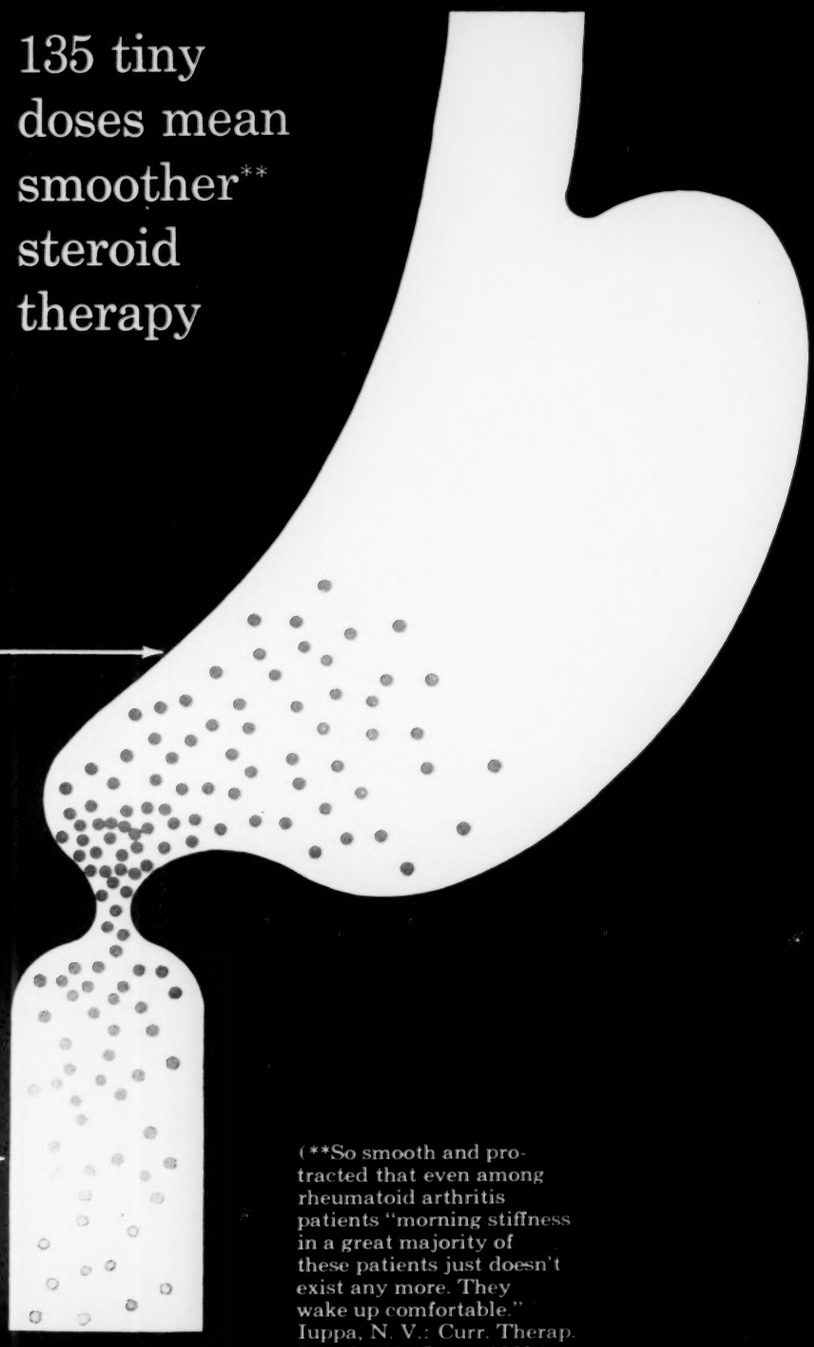
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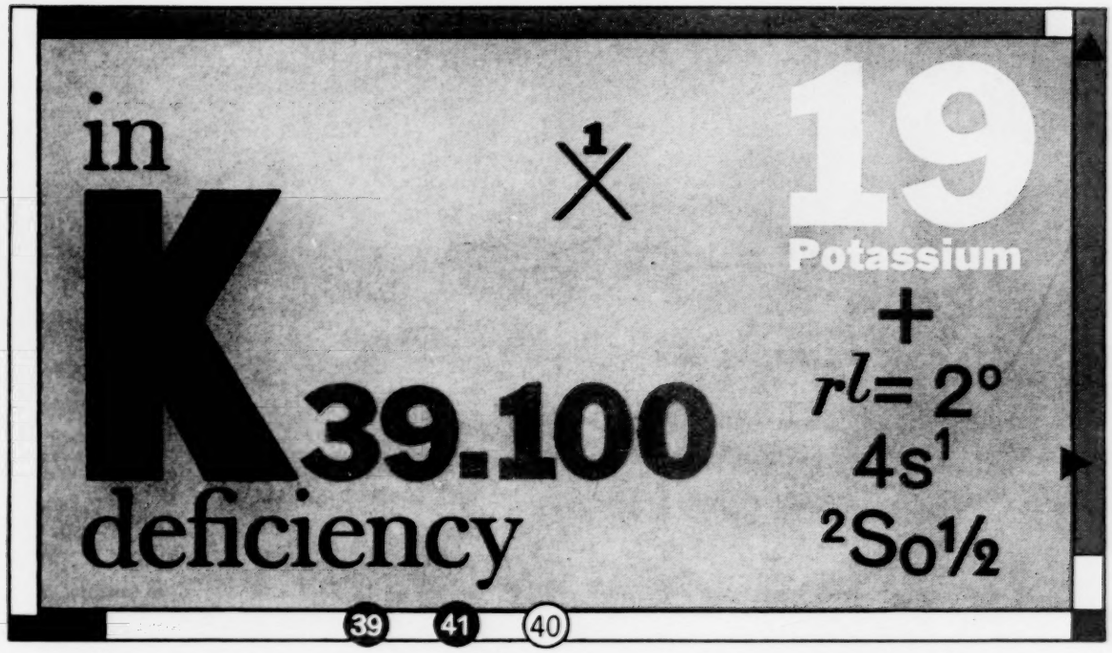
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What better way is there to supply this necessary potassium than for your patient to drink a glass of orange juice each time he takes his medication? . . . What pleasanter source of potassium than delicious, refreshing *Florida orange juice* — either freshly squeezed, frozen, or canned? In any form orange juice is rich in potassium and vitamin C. For the heart failure patient it's important, too, that supplementary potassium tends to reduce the intensity of sodium retention and lessens the threat of edema.

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ADDITIONAL DATA

On the comparison of Potassium Penicillin V and Synthetic Penicillin

1 *On antibacterial activity in the serum*

In a recent, follow-up study[1] involving a number of penicillins, McCarthy and Finland compared the antibacterial activity of potassium penicillin V and synthetic penicillin. They wrote: "Penicillin V provided greater activity than phenethicillin [synthetic penicillin] against the streptococcus and pneumococcus, at least equivalent activity against staphylococcus and sarcina in the serum and the same or greater activity in the urine although the concentrations of phenethicillin were higher and a slightly greater proportion of the latter was recovered from the urine."

In other comment on the two penicillins, they stated: "Thus, although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess . . . "

In an earlier study[2], the same investigators found that the two penicillins "are absorbed in essentially the same manner in normal men and produce comparable levels of antibacterial activity in the serum."

A direct laboratory comparison[3] by Abbott scientists revealed a measurable difference in activity, milligram for milligram, between the two penicillins *in vitro*. Against four pathogenic strains (staphylococcus, streptococcus, pneumococcus, and corynebacterium species), potassium penicillin V exhibited from two to eight times the antibacterial activity of synthetic penicillin. In another study, Griffith[4] found that penicillin V not only produced peak levels of serum antibacterial activity faster, but produced values almost half again as high as those obtained with synthetic penicillin.

2 *On resistance to penicillinase*

In another recent report, Geronimus[5] commented on this aspect of the new penicillin. He concluded after analyzing the current data: "Very large concentrations of alpha-phenoxyethyl penicillin (phenethicillin or penicillin-152) were required to inhibit even so-called moderately penicillin-resistant staphylococci when populations were employed that approached those found *in vivo*. Inferences regarding the possible effectiveness of phenethicillin in infections by penicillinase-producing staphylococci drawn by others from experiments with relatively minute inocula were found to be unwarranted."

McCarthy et al.[2] reached a similar conclusion stating: "Both of these penicillins [potassium penicillin V and phenethicillin] are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus*."

At Abbott, investigators studying the same subject[3], found that the rate of destruction of all three penicillins was so great that any differences were of no therapeutic significance.

3 *On the comparative safety of oral penicillin*

In 1957, a nationwide survey[6] of antibiotic reactions was made. One of the conclusions reached by the investigators in regard to penicillin reactions was: "It is clear also that the oral route is the much safer method of administration, both from the standpoint of numbers

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offers greater antibacterial activity
against penicillin-sensitive organisms

of reactions and of mortality." Neither this survey, nor any evidence presented since, indicates that any form of oral penicillin is less allergenic than another oral form.

4 *On the recent claims of synthetic penicillin*

Recently, the New England Journal of Medicine editorially reviewed the status of the two penicillins.[7] The article concluded: "It thus appears that the major claims of phenethicillin over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-producing staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtue of importance that should impel one to choose over other available forms."

And in England, where synthetic penicillin was first discovered and marketed, the British Medical Journal (after studying a commercial brochure) editorialized: "There is no evidence of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested."[8]

5 *On the advantages of Compocillin-VK*

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1. McCarthy, C. G., and Finland, M., Absorption and Excretion of Four Penicillins, New England J. Med., 263:315, August 18, 1960.
2. McCarthy, C. G., Hirsch, H. A., and Finland, M., Serum Levels After Single Oral Doses of 6-(a-Phenoxypropionamido) Penicillinate and Penicillin V, Proc. Soc. Exper. Biol. Med., 103:177, January, 1960.
3. Laboratory Records, Microbiology Department, Abbott Laboratories.
4. Griffith, R. S., Comparison of Antibiotic Activity in Sera after the Administration of Three Different Penicillins, Antibiot. Med. & Clinical Therapy, 7:129, February, 1960.
5. Geronimus, L. H., Inoculum Size and the Apparent Sensitivity of Staphylococci to Penicillins, New England J. Med., 263:349, August 18, 1960.
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7. Editorial: New "Synthetic" Penicillin, New England J. Med., 263:361, Aug. 18, 1960.
8. Editorial: A New Penicillin, Brit. M. J., 2:940, Nov. 7, 1959.

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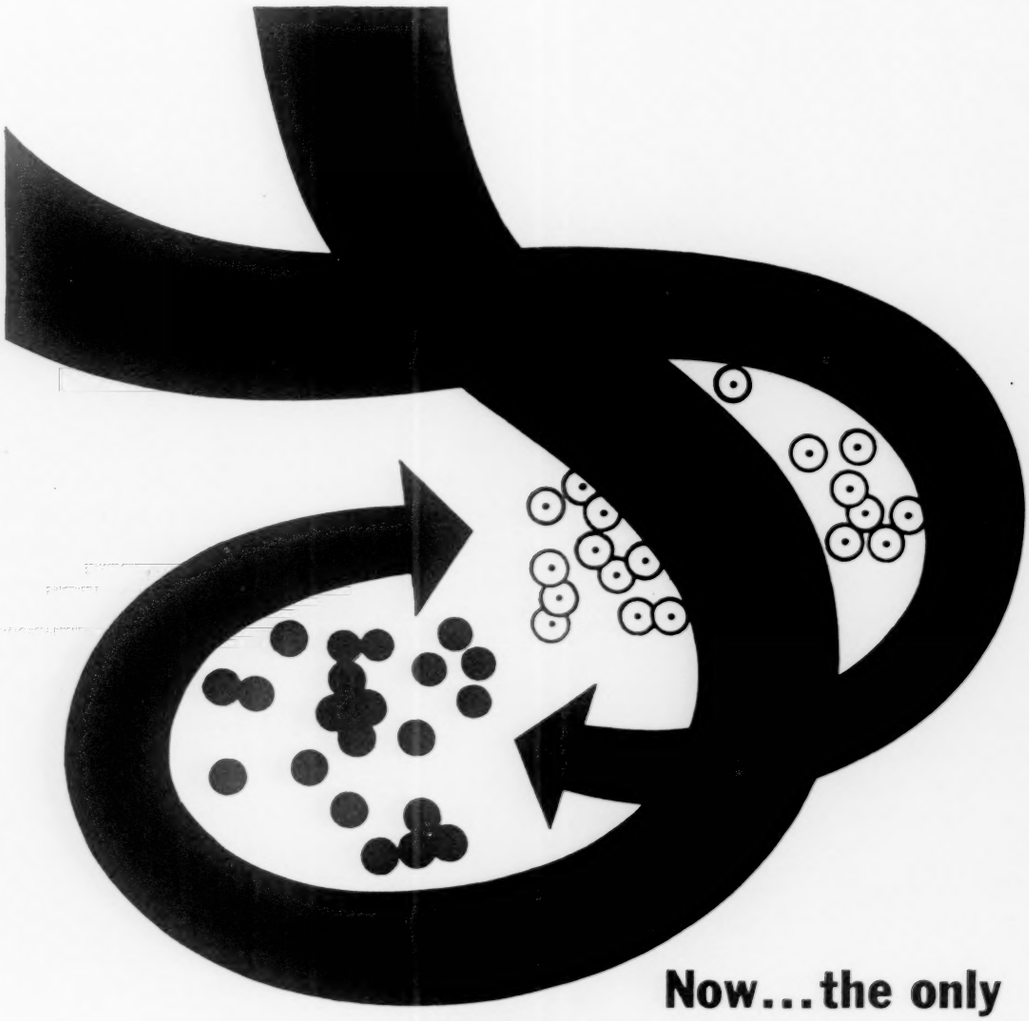
Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

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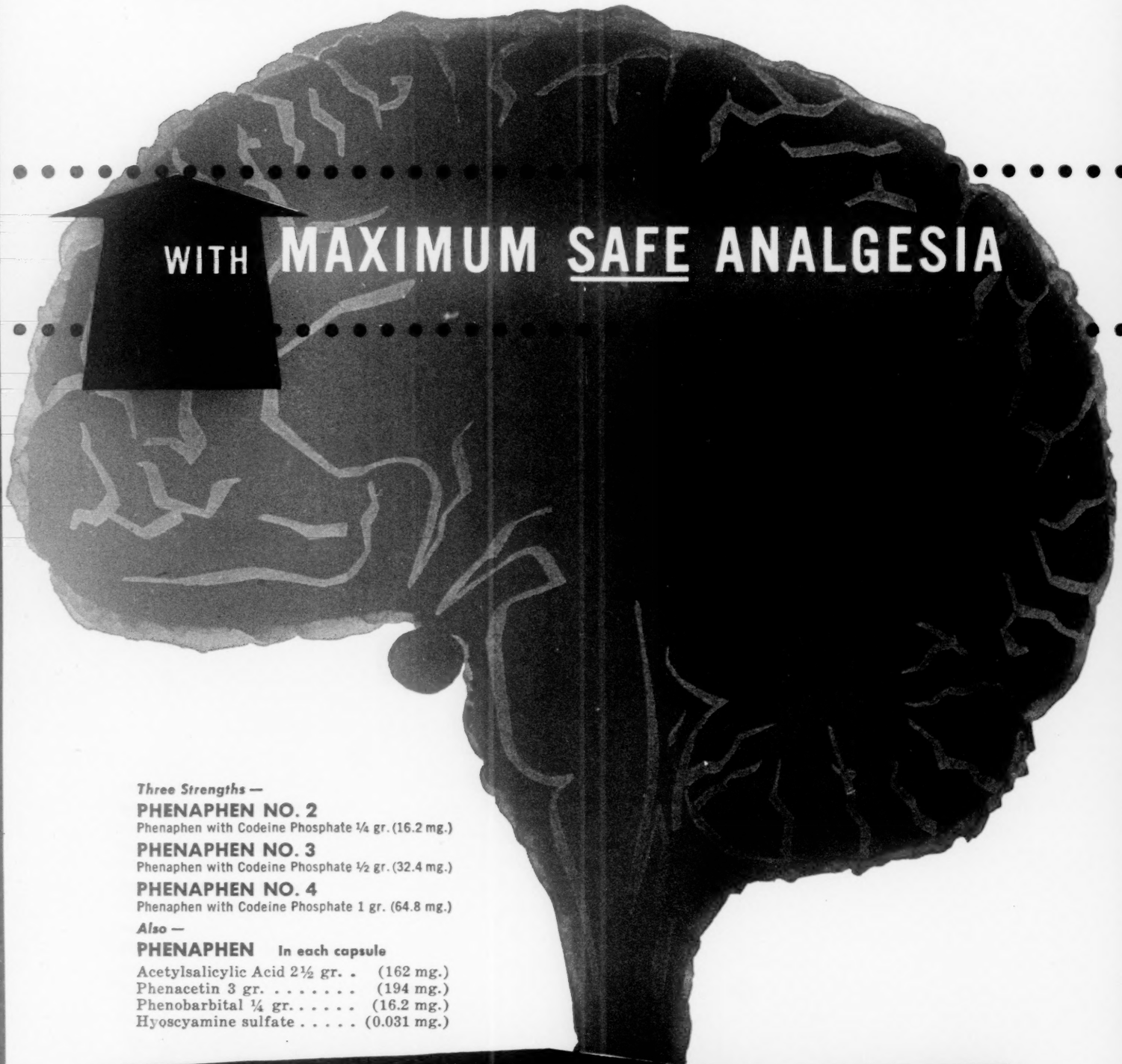
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"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

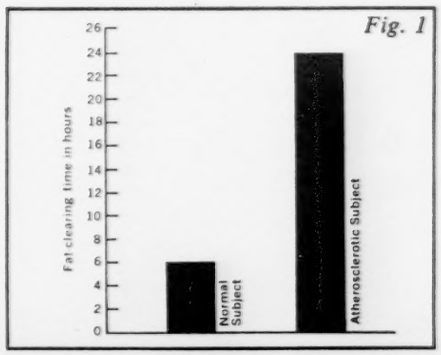
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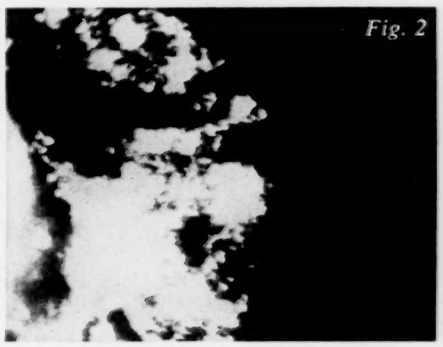
'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

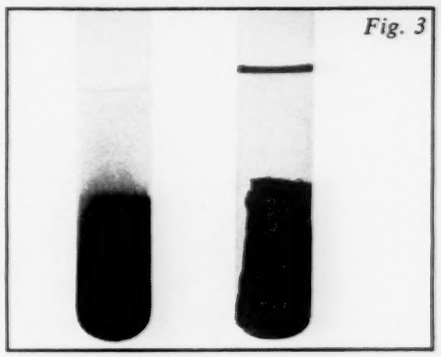
References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology 9:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

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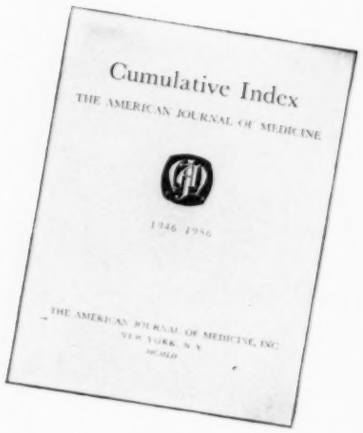
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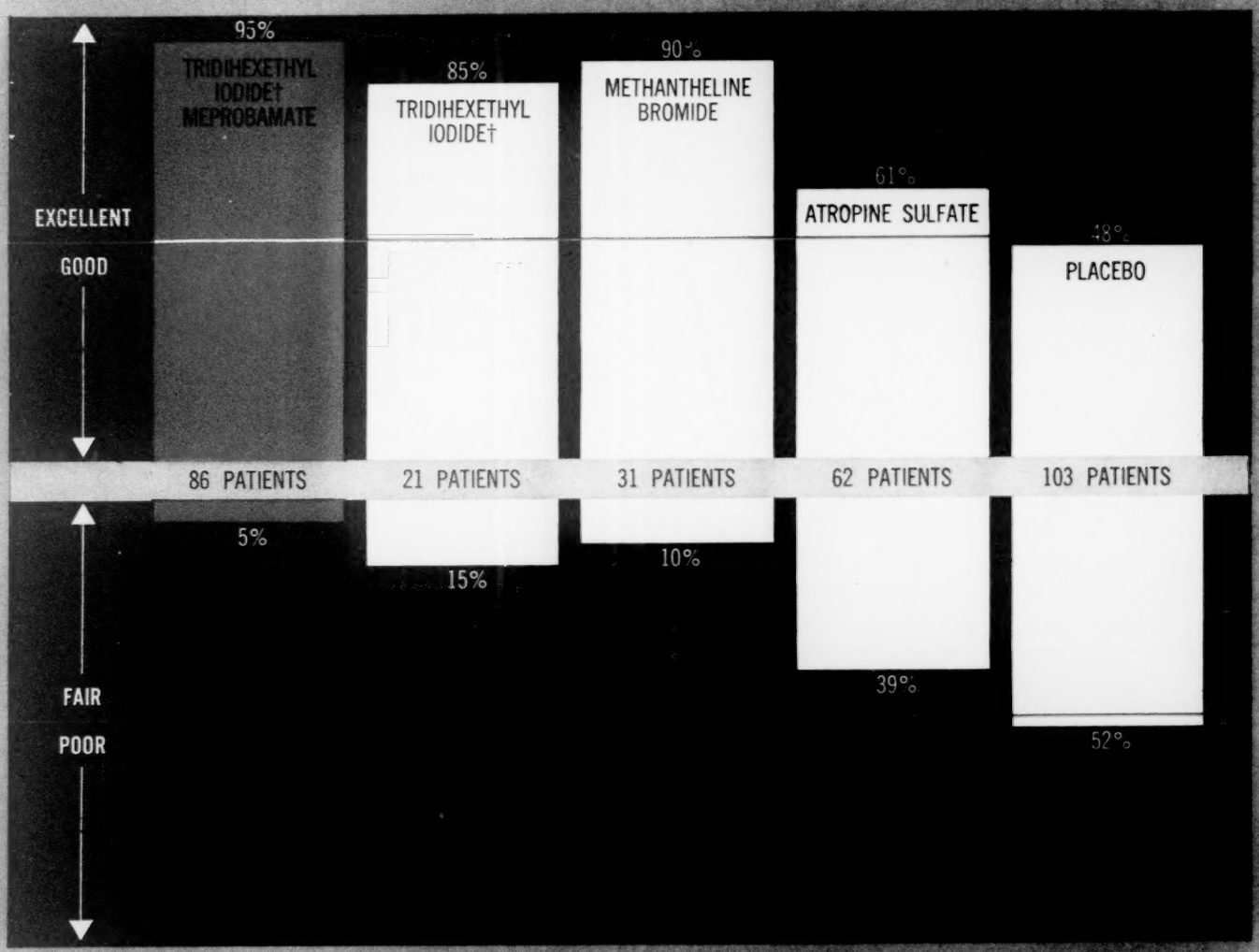
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DROWSINESS	0%	0%	0%	0%
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PERFORATION	0%	0%	6%	0%
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***Atwater, J. S., and Carson, J. M.: Therapeutic Principles in Management of Peptic Ulcer. Am. J. Digest. Dis. 4:1055 (Dec.) 1959.**

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SUMMIT, N. J.

*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955. /2830MB

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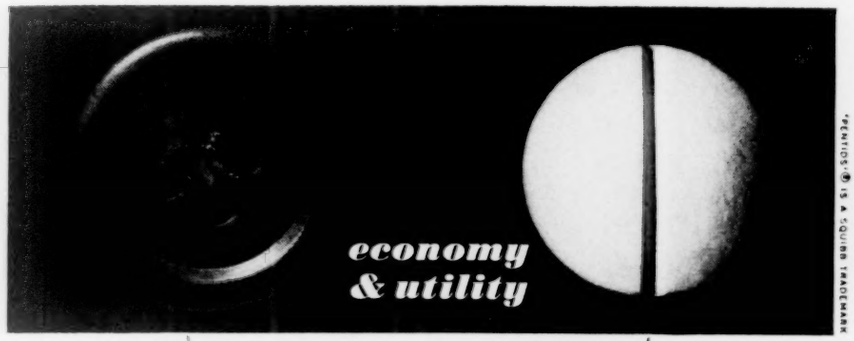
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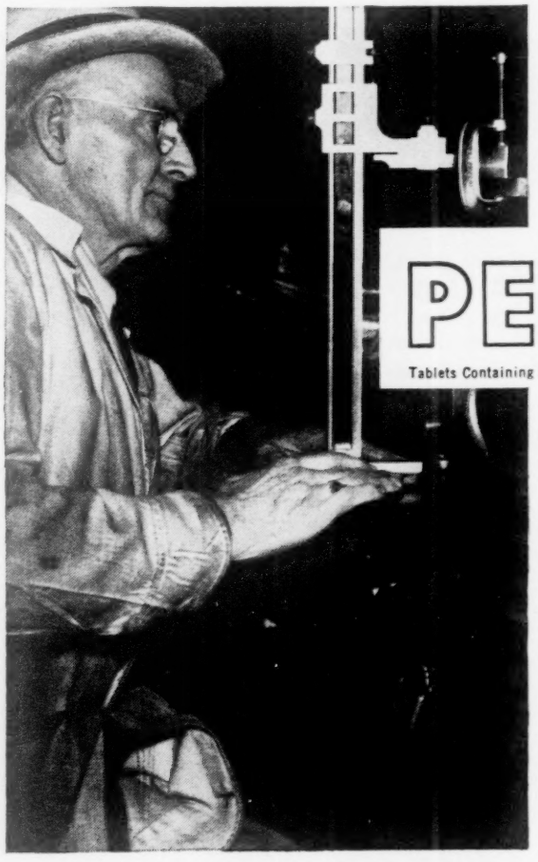
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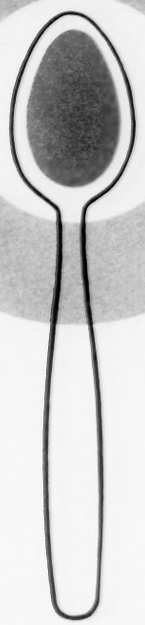
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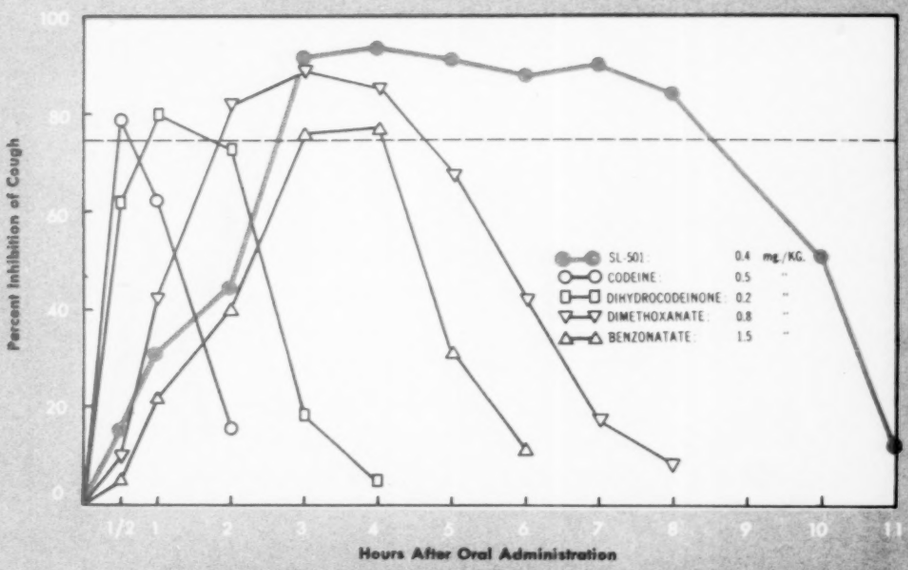
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Chen, J. Y.; Biller, H. F., and Montgomery, E. G., Jr.: J. Pharmacol. & Exper. Therap. *126*:364, 1960.

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in 1078 patients observed by 50 U.S. investigators, 46 of whom were chest physicians

Diagnostic Category	Number of Patients	Results			
		Good to Excellent	Fair	Poor	Not Specified
Upper Respiratory Infection	521	357	88	57	19
Bronchitis	398	309	42	38	9
Pneumonia	53	44	4	5	0
Postnasal Drip	48	32	9	3	4
Tracheobronchitis	32	23	4	3	2
Croup	14	10	2	2	0
Pleurisy	12	11	0	1	0
Total Patients	**1078**	**786**	**149**	**109**	**34**
Total Patients Benefited			**86.2%**		

ADVANTAGES OF ULO

- Uninterrupted sleep... bedtime dose usually carries patient through the night; especially important with children.
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- High therapeutic index.

turn page for indications and dosage information

ULO®

non-narcotic cough suppressant

SYRUP

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Pneumonia
Bronchitis
Tracheitis
Laryngitis
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Pertussis
Pleurisy

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ULO is known chemically as alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol hydrochloride. It acts in a manner similar to that of narcotics, but with a longer span of peak activity. In addition, ULO produces mild local anesthetic and bronchial antispasmodic effects.

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2-6 years of age, ½ teaspoonful (12.5 mg.) 3 or 4 times daily as required.



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ULO Syrup, 25 mg. per teaspoonful, in bottles of 12 fluid ounces.

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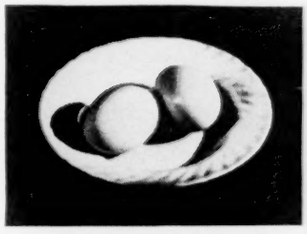
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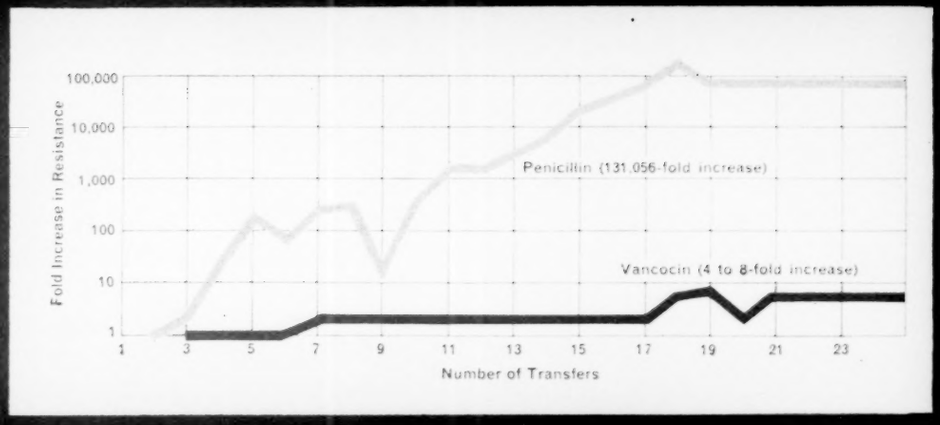
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*David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient, A. M. & C. T 7:364 (June) 1960.

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The American Journal of Medicine

VOL. XXIX NOVEMBER 1960 NO. 5

Symposium on Peptic Ulcer

Introduction

FEW problems in medicine, and surely no others in gastroenterology, have attracted as much interest, investigation and speculation as peptic ulcer. Claude Bernard once wrote: "Even mistaken hypotheses and theories are of use in leading to discoveries. It seems indeed a necessary weakness of our mind to reach truth only across a multitude of errors and obstacles." Peptic ulcer has had its proportion of faulty concepts and confusing hypotheses; and the cause and the pathogenesis are yet to be revealed. Nevertheless, much has been learned of the disorder, its clinical features, course and its management. The purpose of this symposium is to review some of the newer knowledge of gastric secretion and peptic ulcer, and to indicate several current approaches to the problem.

Hogben's scholarly discussion of the molecular events leading to the elaboration of essentially isotonic hydrochloric acid by the stomach deals essentially with the mechanisms for the transport of H^+ and Cl^- ions. Further delineation of the process, according to Hogben, requires knowledge of the electrophysiology of the gastric mucosa and the energy requirements involved in hydrochloric acid secretion. Clearly related to these issues, of course, are the metabolic characteristics of the acid- and pepsin-secreting cells and the factors influencing their function.

Woodward reviews the role of the vagus nerve and of the gastric antrum in the secretion of hydrochloric acid. The more probing the investigation of gastric secretory mechanisms, the more evident is the interrelationship between the various components of the process. The cephalic, gastric and intestinal phases, demonstrable individually under appropriate experimental conditions in animals, function integrally, as a unit. Until recently, chemical and mechanical stimuli were regarded as the sole mediators of the gastric phase. Nyhus now presents evidence for the role of the vagus nerve in the function of the antrum, in addition to the independent activity of this structure. These findings may have important implications in the surgical management of peptic ulcer; but more significantly, perhaps, they demonstrate that, despite intensive study, our knowledge of gastric secretion is far from complete. This point is further emphasized by Clarke, who directs attention to the peptic ulcers associated with cirrhosis of the liver; to the increased secretory response to histamine in dogs with portacaval shunts; and to the evidence for another humoral agent increasing gastric secretion, demonstrable under conditions of portacaval shunt. This secretory substance is increased by feeding, especially of protein, is decreased only slightly by antibacterial action upon the intestinal flora, and appears to originate in both the small and large intestine.

Grossman's paper indicates that, except for the excessive gastric secretion in many patients with duodenal ulcer, other measurable parameters of gastrointestinal function do not differ significantly from the normal. The problem involved here probably is lack of appropriate technics for differentiating the patient with peptic ulcer from the patient without peptic ulcer, biologically and biochemically. Of interest is the association of peptic ulcer with blood group O, the absence of ABH substances in the saliva of patients with

duodenal ulcer, and the hypersecretion of another blood group material, Lewis substance, in patients with ulcers. The secretion of blood group or other antibody substances in gastric and intestinal secretions has not been studied sufficiently and would appear to be of considerable interest. These observations emphasize the potential importance of genetic influences in peptic ulcer, perhaps in relation to such questions as tissue resistance and individual vulnerability.

The geographical and environmental influences in peptic ulcer, another important source of information, also have not been investigated fully. Peptic ulcer is world-wide in distribution, with variations from place to place in incidence, sex ratio and preponderance of duodenal or gastric ulcer; and it occurs under a great variety of external circumstances. Yet the biological response of the end organ, man, presumably is similar everywhere. The nature and dynamics of this response are not well understood, and, indeed, have been investigated only occasionally and incompletely, probably because of technological limitations. This approach to the ulcer problem would seem to be one of the most significant, yet most complex.

The papers by Zollinger and by Gray describe the ulcers associated with non-beta cell, non-insulin secreting adenomas or diffuse hyperplasia of the pancreatic islets and with parathyroid hyperfunction, respectively. The "pancreatic adenoma ulcers" are characterized clinically by enormous gastric hypersecretion, atypical location, multiple complications, and by refractoriness to all types of medical management and to surgical treatment, short of total gastrectomy. In addition to the pancreas and parathyroids, adenomas of the adrenal cortex, pituitary gland, and possibly the thyroid may be involved; in fact, multiple adenomas are not unusual. There is no evidence at present relating the usual peptic ulcer to such endocrine influences, nor is it certain that the "endocrine ulcers" represent an homogeneous entity. However, the study of these unusual lesions may provide important clues to the general problem. The tremendous output of hydrochloric acid in the "endocrine ulcer" is not ascribable to vagal and antral mechanisms. Of interest in this connection is the recent extraction of a humoral substance from a pancreatic adenoma, closely resembling gastrin. Noteworthy also is the apparent stimulation of acid secretion by pancreatic secretion given intravenously. Further investigation of this question and the re-study of humoral agents such as enterogastrone and uroanthelone, with newer technics, also may be informative. The evidence implicating parathyroid hyperfunction with an increased frequency of peptic ulcer seems less impressive statistically, although such a relationship may exist, and the individual cases are most intriguing and suggestive. If valid, the nature of the ulcerogenic mechanism in parathyroid "endocrine ulcers" is even more obscure; for the tremendous gastric hypersecretion is lacking in these patients.

The extensive review of ulcerogenic drugs by Segal provides a comprehensive list of therapeutic agents capable of aggravating or initiating gastric and duodenal ulcers in man. Apart from the practical value of this information, the drug-induced ulcer represents another potential source of information on the problem. The essential role of hydrochloric acid and pepsin in the development of peptic ulcer, including drug-induced ulcers, has been well documented. In studying the tissue component of the process, attention should be directed to the local chemical and biological effects of these compounds upon the gastric mucosa. At this point, the clinical frequency of ulcers and the many experimental technics for their production may suggest that the critical problem is not so much the occurrence of peptic ulcer, but rather its non-occurrence! Careful investigation of persons with apparent resistance to peptic ulcer may, indeed, prove to be a useful approach, but appropriate methods for studying this intriguing question seem to be lacking at present.

The final paper of the symposium re-emphasizes the important principles in the management of peptic ulcer and its complications. While no significant advances in treatment have emerged in recent years, a detailed account of acceptable therapy seems justified by the generally casual and ineffective approach to this problem. Despite the limitations of conventional therapy, careful medical management is highly effective in the healing of active ulcer. The continued appearance of new ulcer "cures" reflects the careless therapeutic attitude toward peptic ulcer now prevailing, as well as the uncontrolled, over-enthusiastic evaluations.

In reflecting upon the total problem, many apparently diverse yet interrelated factors seem

to be involved in the pathogenesis of peptic ulcer. The approach, therefore, must be comprehensive. In addition to the study of gastric secretion, increased attention should be directed to the factor of tissue resistance, the vascular dynamics of the stomach and duodenum, neurogenic, humoral and genetic influences upon gastrointestinal physiology and function, and to the biochemical and immunochemical characteristics of the epithelial cells of the gastroduodenal mucosa. Most important of all may be further study of the responsiveness of man and his stomach to his environment. Progress has been slow, but the continued advances in medicine and science, by providing the necessary technics for investigating these and related problems, should facilitate the search for the cause and the cure of peptic ulcer.

JOSEPH B. KIRSNER, M.D.
and WALTER L. PALMER, M.D.
Department of Medicine,
University of Chicago,
Chicago, Illinois

Formation of Hydrochloric Acid by the Stomach*

The Current Status

C. Adrian M. Hogben, M.D.
Washington, D. C.

The following is a brief summary of the present state of our knowledge or, if you prefer, our condition of ignorance of the molecular events that lead to the elaboration of isotonic hydrochloric acid by the stomach. This topic has been the subject of critical reviews [*1,2*] and has been presented from several different points of view [*3–11*]. Confronted with this wealth of commentary, we should perhaps start with a statement of the problem and the variables involved.

The careful chemical analyses undertaken during this century have established that the composition of uncontaminated gastric juice is a function of its rate of formation. When the rate of formation is slow, the composition approaches that of isotonic sodium chloride. When the rate is brisk, the composition of the juice approaches isotonic hydrochloric acid. Two schools of thought have sought to explain why the composition of the juice is a function of its rate of formation. On the one hand, it has been suggested that the final composition is an admixture of secretions, one neutral and the other isotonic hydrochloric acid [*12*]. Alternately, the disappearance of hydrogen ion from sparsely formed juice has been attributed to its passive escape back through the mucosa and its replacement by sodium ion [*13*]. This controversy has not been spectacularly profitable; it has not been resolved nor are the alternatives mutually exclusive. Nevertheless partisans to both sides of this controversy agree that the central problem is one of explaining the elaboration of essentially isotonic hydrochloric acid.

Ever since Prout in 1824 identified muriatic acid in gastric juice, interest has centered on the transfer of hydrogen ion across the gastric mucosa. This focus of attention hardly needs justification. The H^+ ion concentration is increased by a factor of a million and this high concentration will continue to be regarded as an ever present threat to the integrity of the upper gastrointestinal tract. While we still know very little about the machinery responsible for H^+ ion secretion, it is a transport of H^+ from the interstitial fluid into the gastric lumen. Teorell demonstrated that secretion by the isolated stomach results in a stoichiometric disappearance of hydrogen ion from the solution bathing the serosal surface [*14*]. In current jargon the gastric epithelium performs work through a "hydrogen pump."

The careful studies of Davenport disclose, at least for the isolated stomach, that two H^+ ions are secreted for every O_2 molecule consumed [*15*]. Before considering the implication of this ratio further, we should undertake a provisional thermodynamic analysis. The minimum cost of transferring a mole of H^+ ion against a gradient of 10^6 is about 10,000 calories [*3*]. The maximum yield from the combustion of glucose is approximately 100,000 calories per mole of O_2. Thus without going any deeper into the intimate details of the mechanism, secretion of acid can approach a gross efficiency of 20 per cent. The efficiency of the process is such that we expect little help from a popular mode of biochemical investigation, i.e., the use of metabolic inhibitors. The action of any agent interfering with the transfer of energy would not be expected to be any more unique than that of sand bringing a machine to a grinding halt.

But the relation between secretion and respiration has figured most prominently in evaluation of a particular hypothesis of H^+ secretion, the

* From the Department of Physiology, The George Washington University, Washington, D. C.

"redox pump." This model, which has been proposed by a number of persons, developed in detail by Conway [*16*], and reviewed in the light of recent biochemical developments by Robertson [*17*], is so widely accepted that one might be inclined to conclude that it rests on a firm foundation of experiment. The secretion of H^+ ion by a "redox pump" is achieved when substrate atomic hydrogen, SH, is oxidized by an electron acceptor. This reaction occurs at the outer face of the cell membrane bordering the gastric cavity. At the inner face the electron acceptor which is usually thought of as a cytochrome-like compound, Fe, is in its turn oxidized. We can write the reaction at the outer face as:

$$(1)\quad 4\,SH + 4\,Fe^{+++} \rightarrow 4\,H^+ + 4\,S + 4\,Fe^{++}$$

and at the inner face as:

$$(2)\quad O_2 + 4\,Fe^{++} + 2\,H_2O \rightarrow 4\,Fe^{+++} + 4\,OH^-$$

It is important to note that if an electron acceptor is regenerated directly by molecular O_2, no more than 4 H^+ ions can be formed for every O_2 consumed. However, the essentials of the "redox pump," which are the generation of H^+ ions by oxidation and electron conduction in the membrane, do not require the direct and immediate participation of molecular O_2 [*18*]. It can be proposed that a further reaction occurs at the inner face where a hypothetic reactant, LX, brings about a transformation of the substrate:

$$(3)\quad S + LX \rightarrow SX + L$$

such that reaction (1) can be driven in the opposite direction at the inner face:

$$(4)\quad SX + Fe^{++} + H_2O \rightarrow SH + Fe^{+++} + OH^- + X$$

After the products SH and Fe^{+++} rotate in the membrane, reaction (1) would generate H^+ at the outer face. While I have deliberately simplified this scheme and have side-stepped the issue of the free energies involved, I have done so to emphasize that a "redox pump" need not necessarily react directly with O_2. The number of H^+ ions per O_2 need not be restricted to 4 but would be limited instead by thermodynamic considerations.

It is necessary to dwell on these details because the hypothesis of the "redox pump" has been widely accepted and it has been evaluated almost exclusively in terms of the O_2 consumption. In brief, the experimental evidence appears to be (1) a ratio of less than 4 for H^+ secreted to O_2 consumed would be consistent with a redox pump; (2) the ratio is about 2; (3) since even such a low ratio requires a gross efficiency of 20 per cent, it would be unreasonable on thermodynamic grounds alone for the ratio to be much greater than 2; and (4) even if the ratio did exceed 4, this violation would not exclude a redox pump.

Like H^+ the Cl^- appearing in gastric juice is derived from the interstitial fluid which is continuously replenished by the circulation. Less obviously, the Cl^- is also actively transported by the gastric epithelium even though against a lesser gradient. Its concentration is increased from 110 to 160 mEq./L. More significantly, since it is a negatively charged ion, it has to move against an adverse difference of electrical potential because the gastric lumen is 35 mv. negative to interstitial fluid.

While isotopic tracers cannot be used profitably to follow the movement of H^+, use of the radioisotope Cl^{36} has disclosed something about the nature of the "chloride pump." The isotopic movement or flux of Cl^- in the direction counter to secretion, or from lumen to interstitial fluid, is much greater than a knowledge of the electrical conductance of the gastric mucosa would lead one to predict [*19*]. This unexpected observation can be explained by postulating that Cl^- forms a nonionized chemical complex which permits isotopic exchange but does not constitute a path for free ionic diffusion. The presence of such a carrier is also suggested by the finding that the isotopic flux from interstitial fluid to lumen is dependent on the Cl^- concentration at the luminal surface [*20*]. Interestingly enough dinitrophenol, which of course blocks the transport of both H^+ and Cl^- by disrupting the transfer of energy, also reversibly decreases the carrier exchange of Cl^- [*20*]. Now if one not only follows the transfer of Cl^{36} between the two solutions bathing the mucosa when one side is exposed to the isotope but also measures the intracellular specific activity, one can determine separately the exchange of Cl^- across each face of the gastric epithelium. In the absence of dinitrophenol, the exchange across the luminal face is some twenty times greater than the exchange across the interstitial face of the gastric epithelium. After inhibition the previously

preponderant exchange at the luminal surface decreases to become one-half the value at the interstitial face which remains virtually unchanged [*21*]. This leads to a conclusion that a major part of the carrier exchange is located in the cell membrane bounding the lumen, and by inference the "chloride pump" is also located in this same membrane.

Although there may be species differences, and quite clearly the kinetics of transfer are complicated, it is evident that the "chloride pump" is not distinguished by an exceptional degree of specificity. It should perhaps be spoken of as a "monovalent anion pump" since it can actively transport Br^-, SCN^-, I^- and NO_3^-, though these other anions are transported less avidly than Cl^- [*22*].

But as to the nature of the "chloride pump" we are as much in the dark as we are in reference to the "hydrogen pump." It is possible that the "redox pump" which we have just considered is also responsible for the active transport of Cl^-. It is only necessary to stipulate that Cl^- is linked to the extra positive charge of the electron acceptor as it rotates from the inner to the outer face of the cell membrane. Just as in the case of H^+ ion transport, there is no evidence either for or against the suggestion that a "redox pump" is responsible for the active transport of Cl^-. However, if Cl^- is transported by a "redox pump," it is unlikely that the pump is driven directly by molecular oxygen. We have noted that two H^+ are secreted for every O_2 molecule consumed. When the isolated frog gastric mucosa is electrically short-circuited, three Cl^- ions are transported for every H^+ [*10*]. So unless the maneuver of short-circuiting the mucosa increases oxygen consumption, six Cl^- would be transported for every O_2 molecule utilized.

A quite different scheme has been proposed for the active transport of Cl^- [*23*]. Active transport of Cl^- could be accomplished by the forced exchange of Cl^- for HCO_3^-. At the inner face a hypothetic carrier would have a high affinity for Cl^-; but when it rotated to the outer face, it would acquire a greater affinity for HCO_3^-. Necessarily this carrier would have to be modified by other reactions which would result in the crucial transfer of energy. The result would be that Cl^- would be secreted into the lumen; and if HCO_3^- were continually restored by the diffusion of CO_2, H^+ would also accumulate in the lumen. In other words, there would be secretion of HCl. If part of the HCO_3^- diffused back into the lumen, it would give rise to an electrical potential difference having the same orientation as the potential difference normally occurring. Attractive as this model is, it cannot be accepted without resolving several questions [*4*].

More recently the work of Heinz and Durbin has challenged the essential premise of both models that we just mentioned [*24*]. Both propositions employ only one pump to account for the secretion of H^+ and Cl^-. These investigators have studied H^+ secretion by the isolated gastric mucosa when it is bathed by a salt solution of which the principal anion is $SO_4^=$ instead of Cl^-. When electrically short-circuited, the gastric mucosa is able to secrete H^+ even though there is no evident secretion of anion. On the face of it, and I see no obvious objections, we must accept the conclusion that the "hydrogen pump" can operate independently of the "chloride pump." This hardly allows us to suggest that hydrogen ions are generated by forced anion exchange. But before I abandon an apparently lost cause, I should like to draw upon the general fund of biologic knowledge. The sulfate ion is associated with H^+ transfer in at least two striking circumstances. It is claimed that the mollusk, Dolium galea, has digestive glands that secrete 5 per cent sulfuric acid [*25*] and certain tunicates are reputed to have circulating corpuscles with an internal pH of 2 in association with a high concentration of $SO_4^=$ [*26*]. If it were not for these instances and the observation that at least two anions, SCN^- and NO_3^-, actually interfere with the process of H^+ secretion, I would accept the authors' interpretation as unhesitantly as I accept their findings.

This brings us to the point where we have to consider the possibility of two pumps being responsible for the secretion of hydrochloric acid, a "hydrogen pump" and a "chloride pump." Acting in concert or independently, these mechanisms have to be considered in electrical terms for they operate on charged particles. In most vertebrate species that preempt attention, the gastric mucosa not only secretes HCl but it also generates a significant potential difference such that the gastric lumen is 35 mv. negative to the interstitial fluid. This association has prompted Rehm to suggest that the mucosal potential is a fundamental feature of the mechanism responsible for HCl secretion [*11*]. The origin of this mucosal potential is now understood. It is the result of the "chloride

pump" transferring more negatively charged ions per unit time than positive ions are transferred by the "hydrogen pump" [*19*]. The difference, which constitutes a current of negative ions, generates the mucosal potential. If the transmucosal potential is increased or decreased experimentally, the rate of H^+ secretion is changed in a parallel fashion [*27*]. This might indicate that the gastric mucosal potential controls H^+ secretion directly and serves to integrate the secretion of H^+ and Cl^-. But before we reach the conclusion that the potential difference directly modulates a "redox pump," we must take cognizance of the observation that a sustained alteration of the potential difference brings about changes in the epithelial intracellular ionic composition which may not be inconsequential. It should also be emphasized that the H^+ secretion does continue after the potential difference is abolished electrically or by a carbonic anhydrase inhibitor [*4*]. What may be a more dramatic challenge to the premise that the gastric potential is a fundamental part of the machinery responsible for the formation of HCl is the finding that the elasmobranch fishes, though quite able to secrete HCl, do not develop the distinctive potential difference encountered in other vertebrates [*28*].

If it is not clear that the gastric potential is a necessary feature of HCl formation, the presence of a potential does point to an important unresolved problem. Apart from the abrupt change in potential associated with the onset of secretion, the potential difference remains constant from the slowest to the most rapid rates of secretion. On analysis it has been determined that the membrane resistance also remains essentially constant, indicating that the short circuit current does not vary in spite of large changes in the rate of secretion [*29*]. It should be remembered that the short circuit current is a measure of the Cl^- ions transported in *excess* of H^+. Consequently, when the rate of secretion is increased, not only does the rate of Cl^- transport increase but it continues ahead of H^+ by a *constant* amount. It can be pointed out that this would obtain if instead of a "hydrogen" and "chloride pump," that we have already referred to, there were a "hydrochloric acid pump" and an "electromotive chloride pump" [*30*]. Since this is such an elaborate invention, it does not have any vocal advocates. I bring this to the forefront to emphasize that no explanation of the secretion of hydrochloric acid will be complete unless it also clarifies the electrophysiology of the gastric mucosa.

What is certain is that the gastric epithelium does actively transport both the H^+ and Cl^- ions. It is by no means certain that there are two quite separate mechanisms responsible for their transport, let alone the possibility that they are transported by different cell types. But the secretion of these ions, although imperfectly understood, may be sufficient to account for the secretion of the solution—hydrochloric acid. Transported across the gastric mucosa, they would establish an osmotic gradient which could pull water into the lumen. Although it is not proven that the flow of water is simply a passive consequence of the secretion of the ions, it is most probable. Like most other cell membranes, those of the gastric epithelium are relatively permeable to water. The cost in energy of having to transport water itself in the face of this permeability would be prohibitive. So far, nowhere in living systems has anybody succeeded in demonstrating an active transport of water that is not secondary to the transport of solute. There is, however, an apparent active transport of water across the gastric mucosa which is similar to that occurring across the small intestinal epithelium. In order to halt the flow of water across the spontaneously secreting isolated stomach it is necessary to reduce the osmolarity of the solution bathing the mucosal surface by some 100 mOsm less than that bathing the serosal surface [*31*]. Thus during secretion, water moves from a more concentrated to a more dilute solution. This movement ceases when H^+ secretion is inhibited. The probable explanation may seem superficially trivial but it does carry the implication that the fine structure of the epithelial brush border may become increasingly important as we attempt to clarify the events of transport. Due to restricted diffusion the conditions at the site of secretion may differ significantly from those in the bulk solution bathing the mucosa.

Gastric juice also contains as a minor constituent the potassium ion, which is ordinarily present in a concentration of about 10 mEq./L. Recent work from two laboratories indicates that there are still considerable gaps in our knowledge. Harris and Edelman have found that the K^+ concentration of the solution bathing the interstitial surface of the mucosa inversely alters the mucosal potential difference and directly influences H^+ secretion [*32*]. The

contributions from Mount Sinai Hospital of New York disclose that there are striking transient changes in the K^+ concentration of gastric juice upon initiation of secretion, contrary to the belief that the K^+ is essentially constant [*33*]. At the moment we can only remark that these observations constitute a challenge and have yet to be developed to the point where they provide clues to the better understanding of the formation of HCl.

In an era when the biochemistry of enzymes rightly receives so much attention, this commentary may be regarded as inadequate. Omission of the possible enzymes that participate in the process of secretion is intentional. The central problem is one of understanding how energy is used to accomplish the work of secretion. At least in part, the extraordinary efficiency of the process has blunted inquiry. It is reasonable to suppose that much of the metabolic machinery common to all cells is employed in the process. But what parts and to what extent remains a problem for the future. In frustration we turn our attention to those enzymes that are more peculiar to the gastric mucosa: urease and carbonic anhydrase. The first has to be mentioned for historical reasons. Conway advanced the argument that gastric urease has a protective role in the gastric epithelium [*3*]. The appropriateness of this proposal was discredited when it was found that antibiotic therapy eliminated urease activity and most of us accepted the conclusion that the urease was of bacterial origin [*34*]. More recently Conway has challenged the conclusion that gastric urease is indeed bacterial [*35*]. The interested reader will have to draw his own conclusion.

No commentary would be complete without an allusion to carbonic anhydrase. It is there and it has an important though not obligatory role in the formation of HCl. The potent carbonic anhydrase inhibitor, acetazolamide, when administered in quite large doses will inhibit the formation of gastric juice substantially but not completely [*35*]. There is even a tidy explanation for how carbonic anhydrase might work. If the "hydrogen pump" operates only in the cell membrane bordering the lumen and is not present in the membrane separating the cell interior from interstitial fluid, the continued secretion of H^+ must inevitably lead to an accumulation of OH^- within the cell which could not be compensated by intracellular buffers. At any normal pH the concentration of OH^- would be insufficient to provide for the escape of OH^- by passive diffusion with sufficient rapidity. However, HCO_3^- is present in sufficient concentration to allow it to diffuse out the cell into the interstitial fluid at a rate that could match the secretion of H^+ ion into the lumen, provided that the cell membrane is sufficiently permeable. In such a scheme, carbonic anhydrase obviously facilitates the conversion of OH^- to HCO_3^-, using both endogenous CO_2 and CO_2 withdrawn from the blood. This popular hypothesis is strengthened by two and only two important lines of evidence: (1) carbonic anhydrase is present in gastric parietal cells and (2) inhibition of carbonic anhydrase interferes with the formation of HCl.

In conclusion, I think we can say that the formation of hydrochloric acid is the result of the active transport of the two ions, H^+ and Cl^-. I am not confident that we can decide at this time whether this is accomplished by a single mechanism or two separate mechanisms. Regrettably, the molecular events responsible for the secretion of hydrochloric acid are still obscure.

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Vagal and Antral Mechanisms in Gastric Secretion*

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THE nervous, cephalic or psychic phase of gastric secretion is transmitted by the tenth cranial nerves, the vagi. The vagus nerves constitute the entire cranial outflow of the parasympathetic nervous system. The anatomic relationship to the stomach is, as in other parts of the vegetative nervous system, a dual neuron system with a central and a peripheral ganglion, the latter located actually in the wall of the stomach. The parasympathetic system is cholinergic, with acetylcholine the chemoeffector; both the secretory and motor effect of the vagus on the stomach can be duplicated by acetylcholine and other cholinergic drugs.

ROLE OF THE VAGUS

Nervous regulation of gastric digestion was a highly controversial subject throughout the nineteenth century with physicians, relying on clinical observations, presenting the "pro," and physiologists, depending on laboratory experimentation, holding mainly to the "con" view. Although Brodie [*1*], in 1814, demonstrated that section of the vagi in animals suppressed gastric secretion, his study was not widely accepted. It remained for the classic experiments of Pavlov, reported in 1889, to establish beyond question the role of the vagus in gastric secretion [*2*]. He prepared a dog with cervical esophagotomy and gastric fistula. When the animal was fed, ingested food escaped through the opening in the neck and did not enter the stomach. Pavlov called this "sham feeding" and it was followed within five minutes by a copious flow of highly acid gastric juice from the gastric fistula. After section of the vagi the animal "sham fed" as readily as before but no gastric secretory response ensued.

This experiment of Pavlov has remained a classic not only because of the basic nature of his discovery but also because of clarity of concept and simplicity of design. Pavlov's great technical skill as a surgeon was also an important factor in the success of this and other experiments. Pavlov had worked with the German physiologist, Heidenhain, in 1877 and had learned the latter's technic for forming an isolated pouch from the greater curvature of the stomach. Later, in his own laboratory, Pavlov modified the vagally denervated Heidenhain pouch with the preservation of vagal innervation by leaving a seromuscular connection between the main stomach and isolated pouch. It was with this preparation that Pavlov performed his subsequent studies on the conditioned reflex.

The major shortcoming of the Pavlov pouch is the paucity of its vagal innervation since only a few small fibers traverse the seromuscular bridge. Dragstedt developed a technic for isolating the entire stomach of the dog with preservation of its entire vagal innervation [*3*]. The nervous phase is much more prominent in this preparation.

It is interesting that Beaumont did not describe the nervous phase of gastric secretion in Alexis St. Martin, his subject with the accidental gastric fistula. Beaumont thought gastric secretion occurred only when food entered the stomach. The nervous mechanism in man was first described by Carlson in 1916 in a subject with a lye stricture of the esophagus and a surgically created gastric fistula [*4*]. Mastication of palatable food caused the typical "sham feeding" response but the sight or smell of food was observed to have little effect.

Although sham feeding can be achieved in intact human subjects, the nervous mechanism of gastric secretion can be more readily activated by insulin-induced hypoglycemia. Mild hypoglycemic shock is produced with an intravenous

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dose of crystalline insulin and the gastric secretory response occurs when the blood sugar falls to 50 per cent or less of the fasting level. The response is completely abolished by vagotomy and can therefore be used as a test for the presence of vagal innervation to the stomach in both man and experimental animals.

Experimental evidence conclusively proves that a hypersecretion of acid gastric juice will often result in typical chronic peptic ulcer formation. Dragstedt's totally isolated stomach pouch with the vagi preserved secretes large volumes of gastric juice and peptic ulcers frequently form in the wall of the pouch [*5,6*]. If, on the other hand, the vagi are severed in isolating the stomach, as in the preparation used by Lim, Ivy and McCarthy [*7*], only small volumes of juice are secreted and ulcers are rarely if ever observed.

In 1944, Dragstedt and co-workers [*8*] reported that an excessive continuous secretion of gastric juice occurred in patients with duodenal ulcer and that this was reduced to normal or subnormal levels by division of the vagus nerves just above the diaphragm. Basal gastric secretion was studied in human subjects by the introduction of a nasogastric tube and continuous aspiration during a nocturnal twelve hour period with the patient in the fasting state and shielded from the sight and odor of food. This observation was confirmed and extended by Levin, Kirsner, Palmer and Butler [*9*] who found that patients with duodenal ulcer secreted approximately four times as much hydrochloric acid in the basal state as did normal individuals. They also observed that patients with gastric ulcer did not manifest this hypersecretion but actually secreted somewhat less gastric juice than did normal volunteers.

A considerable body of evidence indicates that the hypersecretion associated with duodenal ulcer is of nervous origin. First, the ecology of the disease indicates the importance of occupation, responsibility, social and economic achievement and other situations provoking emotional and nervous tension. Secondly, the hypersecretion is abolished by vagotomy and is readily inhibited by anticholinergic drugs. Thirdly, numerous observations record the effect of emotionally stressful situations in exaggerating the hypersecretion.

The stomach of a patient with a duodenal ulcer contains an excessive number of parietal cells [*10,11*]. Whether this is the cause or effect of hypersecretion remains undetermined. Presumably this could represent work hyperplasia from continued nervous stimulation. On the other hand, a genetic factor has been implicated indicating that the increased secretory capacity might be hereditary [*12*].

The importance of the nervous phase of gastric secretion in normal gastric digestion remains conjectural. Although Pavlov believed that all digestion was largely the function of the nervous system, this view does not obtain today. Carlson found in his gastric fistula subject that approximately 20 per cent of the daily secretion of gastric juice was due to the nervous phase. However, as will be noted subsequently, the nervous and hormonal mechanisms regulating gastric secretion are not entirely separable.

ROLE OF THE PYLORIC ANTRUM

The possibility that the antrum of the stomach might elaborate a hormone which mediates the gastric or antral phase of gastric secretion was first postulated by Edkins in 1906 [*13*]. He reported studies wherein the intravenous administration of extracts of antral mucosa stimulated gastric secretion. In other studies the antrum was separated from the body of the stomach by a rubber diaphragm. The introduction of food substances into the antrum was followed by the secretion of acid gastric juice in the body of the stomach [*14*]. The presence of a hormonal mechanism was indicated and Edkins coined the name *gastrin* for the antral hormone.

Edkins' observations were followed by four decades of controversy concerning his gastrin hypothesis. Although an active principle of pyloric extracts proved to be histamine, some workers obtained histamine-free extracts of the antrum with gastric secretory activity [*15,16*]. Ivy and Whitlow [*17*] and Priestley and Mann [*18*] were unable to repeat Edkins' experiment with antral perfusion, while Savich and Zeljony [*19*] found stimulation of gastric secretion by this means. Excision of the antrum in animals likewise gave conflicting results; some reports indicated no change in gastric secretion [*20,21*]; others demonstrated a reduction in acidity [*22,23*].

When distal partial gastrectomy was extended to the treatment of duodenal ulcer it soon became apparent that excision of the lesion itself was both difficult and dangerous. In an effort to avoid this hazard the duodenal ulcer was left *in situ* and the distal transection made

through the antrum—the antrum exclusion gastrectomy as popularized by Finsterer [*24*]. This was considered safe since the antrum did not secrete acid. However, beginning in 1938 disquieting reports appeared indicating a high incidence of gastrojejunal stoma ulcers in such patients [*25–27*].

The experience of surgeons with the antrum exclusion operation seemed to refute the predominantly negative physiologic studies which followed the initial report of Edkins; on this basis it was believed that reinvestigation of the problem was warranted. Using the collection technic devised by Dragstedt, Haymond and Ellis [*28*], it was possible to assemble reliable, quantitative data. In gastric pouch preparations very little neutralizing material is present, so that the volume of secretion may be greatly reduced without a corresponding reduction in the concentration of free acid.

Effect of Antrum Ablation on Gastric Secretion. Isolated small stomach pouches of the Pavlov or Heidenhain variety were prepared in a series of mongrel dogs. Using a detachable rubber bladder secured to the cannula by a threaded nipple, continuous daily collections were made of the gastric juice secreted by the isolated pouches. After a period of observation at a constant level of secretion, the animals were reoperated upon and resection of the antrum performed. Following recovery from the second operative procedure, collections of pouch secretion were repeated. These studies showed that resection of the gastric antrum produced an extensive reduction (65 to 95 per cent) in the secretion of acid gastric juice in dogs prepared with Pavlov or Heidenhain pouches [*29–30*]. It was apparent that the major stimulus responsible for the secretion of acid gastric juice by these isolated pouches was in some way related to the presence of the antrum.

Effect of Antrum Transplantation on Gastric Secretion. Antrum-transplant experiments were undertaken in which the antrum was removed from gastrointestinal continuity and reintroduced by stages into the second part of the duodenum. Complete interruption of both the parasympathetic and sympathetic nerve supply to the antrum was thereby achieved. The animal preparation used was the totally isolated stomach pouch with vagi cut, the pouch originally described by Lim, Ivy and McCarthy in their classic demonstration of the intestinal phase of gastric secretion [*7*].

The results demonstrated that, after complete interruption of the extrinsic nerve supply to the antrum and separation of vascular and neuromuscular connections to the remainder of the stomach, the antrum when exposed to the contents of the duodenum powerfully stimulated the body of the stomach to secrete acid gastric juice [*31*]. These facts fulfil the requirements defining a hormonal mechanism, confirming Edkins' original hypothesis, and demonstrate that the antrum of the stomach functions as an endocrine organ.

Acid Inhibition of the Antrum. Sokolov, in Pavlov's laboratory, discovered that the introduction of 0.5 per cent hydrochloric acid into the stomach diminished the secretion from a Pavlov pouch [*32*]. The isolated vagally denervated Heidenhain pouch has been found in the dog to provide a reliable indicator of gastrin production by the pyloric antrum. If, in such a preparation, the antrum is transplanted into the colon, the mucous membrane of the antrum no longer comes in contact with hydrochloric acid secreted by the body of the stomach. This results in a threefold increase in secretion of acid gastric juice by the Heidenhain pouch indicating that the gastrin mechanism had been held in check in its normally acid environment [*31*]. Other studies have shown that any procedure which will reduce or neutralize gastric acidity, such as vagotomy or gastrojejunostomy, will regularly result in excessive release of gastrin [*33–35*].

A surgical technic was devised for isolating the gastric antrum, using the method of Pavlov in constructing a double-layered mucosal barrier [*36*]. In this way the vessels and nerves of the lesser curvature were preserved intact. The pylorus was divided and the proximal end brought to the skin as a cutaneous fistula, providing access to the isolated antrum. The addition of a Heidenhain pouch provided an assay for gastrin.

The isolated, innervated antral pouch is highly susceptible to chemical stimuli, crude liver extract and dilute alcohol being those commonly used [*36,37*]. If, however, the pH of the perfusate is reduced to 1.2, there is no augmentation of secretion from the Heidenhain pouch indicating suppression of the gastrin mechanism. The antrum also readily responds to mechanical distention; this effect is completely blocked by simultaneous perfusion of the antrum with tenth normal hydrochloric acid [*37*].

Although twentieth normal hydrochloric acid (pH 1.3) is also effective, fiftieth normal acid (pH 1.7) is ineffective. The pH of the gastric content can be considered to constitute an autoregulatory mechanism; when the pH falls to approximately 1.5, the gastric phase of gastric secretion is terminated. Failure of acid inhibition undoubtedly explains the high ulcer recurrence rate in patients in whom the antrum exclusion gastrectomy have been performed.

The mechanism by which acid inhibits the antrum remains a subject of some controversy. The experiments reported by Harrison et al. [*38*] and Jordon and Sand [*39*] indicated the possibility that the antrum elaborates a second, antisecretory hormone. Other studies have failed to confirm their findings [*40–42*]. If such a hormone is formed, it does not seem to inhibit gastric secretion reliably in response to stimuli other than gastrin. The recent cross circulation experiments reported by DuVal and Price [*43*] provide further support for the concept that the antrum does produce an antisecretory hormone.

Relationship Between Pyloric Antrum and Gastric Ulcer. Dragstedt states that, whereas the nervous phase of gastric secretion is involved in the pathogenesis of duodenal ulcer, the pyloric antrum and its hormonal mechanism seem to be implicated in benign gastric ulcer [*44,45*]. While the basal or interdigestive secretion of gastric juice is markedly elevated in duodenal ulcer patients, Levin and co-workers have pointed out that basal secretion in gastric ulcer patients is even lower than that in normal individuals [*9*]. The motility of patients with gastric ulcer is also less than normal and many of these patients show prolonged retention of ingested material in the stomach. These data suggest that vagal influences on the stomach are actually suppressed in gastric ulcer. In connection with this Dragstedt reports that seven of 150 patients with duodenal ulcer treated by vagotomy alone subsequently developed benign gastric ulcer [*46*]. In a dog prepared with a vagally denervated Heidenhain pouch, division of the vagus nerves to the remaining stomach causes a marked rise in secretion of acid gastric juice by the isolated pouch [*33,46*]. This effect does not occur if the antrum has been previously resected or if retention and stasis in the stomach are prevented by a surgical drainage procedure. It is apparent, therefore, that the gastrin mechanism is readily exaggerated by the hypomotility and gastric retention associated with diminished or absent vagal innervation. In this situation the digestive secretion of gastric juice is increased while the interdigestive or basal gastric secretion is diminished.

Gastric retention associated with anatomic narrowing at the pyloric outlet also exaggerates the gastrin mechanism and is associated with gastric ulcer. Approximately 20 per cent of patients with benign gastric ulcer have a pre-existing duodenal ulcer of long-standing with demonstrable resultant pyloric stenosis. In a dog prepared with a Heidenhain pouch, pyloric obstruction created by narrowing the pylorus with cellophane tape results in a sharp increase in pouch secretion indicating increased gastrin release [*47*]. Dogs prepared in this fashion often develop gastric ulceration.

The response of gastric ulcer to surgery is also informative. Recurrent peptic ulcer follows surgery for duodenal ulcer with discouraging frequency even after extensive subtotal gastrectomy. However in gastric ulcer, conservative distal partial gastrectomy—in essence, resection of the antrum alone—is almost never followed by recurrence of ulcer. The Billroth I or gastroduodenal reconstruction is particularly hazardous in duodenal ulcer; but even with this more physiologically desirable method of surgery, marginal ulcer does not follow when the patient has had a gastric ulcer. This observation indicates not only the importance of the antrum in gastric ulcer but also demonstrates that surgery is more efficacious for this condition than for duodenal ulcer. It is also of considerable interest, as pointed out by Oi and co-workers [*48*], that almost all benign gastric ulcers occur in the mucous membrane of the antrum or in the zone of transition between antrum and the acid-secreting body of the stomach.

INTERRELATION OF CEPHALIC AND GASTRIC PHASES OF GASTRIC ACID SECRETION

In 1915 Schur and Plaschkes [*49*] first suggested a possible relationship between the cephalic and gastric phases of acid secretion. Further impetus was given to this possibility when in 1933 Straaten of Cologne [*50*] noted that gastric secretion, excited by sham feeding of dogs, markedly decreased after resection of the pyloric region. On the basis of these experiments he postulated that for vagal stimulation of acid secretion to occur at least a portion of the antrum must be present. However, Worobjew

and Volborth [*51*] were unable to confirm Straaten's experimental findings. These latter investigators found that within a few days after antral resection cephalic phase secretion returned. With this divergence of opinion, a controversy was begun which was to last unabated for thirty years.

Uvnas has presented the thesis that "the cephalic phase of gastric secretion is controlled by a combined neurohumoral mechanism identical in principle with that of the gastric phase. The pyloric region plays a major part in this mechanism" [*52*]. Uvnas concluded that a "secretagogue agent" was liberated from the pyloric region during vagal stimulation which in turn acted in an excitatory capacity to potentiate the direct effect of the vagus upon the parietal cells. The work of Uvnas was criticized severely during the following decade [*53,54*]. Yet there is little doubt that this was a major contribution.

Clarification of this confusing issue began with the report of Lim and Mozer [*55*] in 1951, that sham feeding in esophagostomized dogs with gastric fistula produced gastric secretory responses greater in amount and duration than could be explained on the basis of vagal phase alone. Lim and Mozer stated that under these conditions the increased gastric secretory response suggested "peripheral liberation of . . . gastrin." However, these authors were unable to demonstrate increased acid secretion from denervated fundic pouches after isolation of an innervated antral pouch and sham feeding.

Burstall and Schofield [*56,57*] demonstrated that insulin hypoglycemia (vagal stimulation) and sham feeding in dogs caused a small amount of secretion from Heidenhain (vagally denervated) pouches and further postulated that this increase in secretion was likely due to the release of gastrin. Uvnas et al. [*58*] and Anderson et al. [*59*] demonstrated in Pavlov pouches an increased twenty-four hour secretion following exclusion of an innervated antrum from the acid stream. Unfortunately, interpretation of these results was difficult because the excluded antrum was left in continuity with the duodenum, and local mechanical and chemical effects may have entered into the reported results.

Two experimental technics for study of the antrum were developed which played a most important role in clarifying this complicated problem. The first of these was the production of a vagally innervated, isolated antrum [*37,55,60, 61*]. The innervated antrum is separated from the main stomach by a double mucosal bridge and the pyloric end is brought out to the skin as a fistula. Thus the antrum is removed from local chemical or mechanical stimuli; hence, changes in gastrin release, as reflected by a Heidenhain pouch, are presumably the results of vagal stimuli only.

Forrest [*60*] was the first to indicate that baseline Heidenhain pouch secretions may increase significantly after isolation of the antrum. Subsequently, Nyhus et al. [*62*] confirmed this response. This rise in acid secretion is interpreted as a continued release of gastrin by vagal stimuli in the absence of acid inhibition. Woodward et al. [*37*] and Oberhelman et al. [*61*] clearly demonstrated the release of gastrin by insulin hypoglycemia, utilizing the isolated, innervated antral pouch and a Heidenhain indicator pouch. Further, Thein and Schofield [*63*] were able to demonstrate much improved acid secretion from denervated pouches during sham feeding when the innervated antrum was isolated. In view of these experiments there is little doubt that vagal stimulation *does* release the hormone gastrin. The two major phases of gastric acid stimulation *are* interrelated.

The second experimental technic which has proved valuable in determining various facets of vagal gastrin release is antroneurolysis [*64,65*]. This technic of separating the antral mucosa from the submucosa, thus disrupting intramural nerve connections from the vagus, has allowed further study of the problem. Using antroneurolysis, Chapman et al. [*66*] refuted an initial concept that in dogs increased antral motility represented the prime mechanism for release of gastrin by vagal stimulation. These experiments confirmed the work of Thein and Schofield [*63*] who showed a lack of correlation between antral motility and acid secretion from a transplanted fundic pouch.

The relationship between vagally induced motility and vagally induced gastrin release is as yet not completely understood. In the dog insulin hypoglycemia will, after a brief period of inhibition, produce antral hypermotility [*66*]. Contrariwise, Thein and Schofield [*63*] found a decrease in antral motility in dogs with sham feeding. In a series of 150 human patients insulin hypoglycemia uniformly inhibited motility at all levels of the gastrointestinal tract [*67*]. Since vagally induced gastric motility and gastrin release do not appear to be intimately related, it appears that there may be two types of

cholinergic effectors: one which mediates gastrin release and one which mediates motility.

The exact mechanism for release of gastrin is unknown; however, it would appear that the vagus nerves supply fibers directly to the antral mucosa or submucous nerve plexus which, when stimulated, produce release of gastrin. Regardless of the specific mechanisms involved, it has been conclusively shown that gastrin release by vagal stimulation is entirely separable from gastrin release by local antral factors, i.e., chemical and mechanical [*62*]. Since these mechanisms of gastrin release are separable, is the vagal release of gastrin of significance in the over-all spectrum of gastric acid stimulatory mechanisms?

DeVito et al. [*68*] demonstrated that, after antroneurolysis to the main stomach, there was a 20 to 80 per cent drop in twenty-four hour Heidenhain pouch secretion. Since neither antroneurolysis nor extrinsic antral vagal denervation appears significantly to modify gastrin release by chemical or mechanical means [*62,69*], this depression in acid secretion noted after antroneurolysis to the main stomach must, in large part, be due to removal of the vagally induced gastrin production. If this is true, the percentage of total daily gastric acid output from vagally induced gastrin release is much greater than ever before realized. The rise in acid secretion from a Heidenhain pouch following isolation of an innervated antrum indicates that the antrum is releasing gastrin in the absence of local antral stimuli. As previously stated, this hypersecretion is interpreted as the result of continued release of gastrin by vagal stimuli in the absence of acid inhibition.

It has been customary to divide arbitrarily the stimuli for the secretion of acid into cephalic, gastric and intestinal phases. Until recently, chemical and mechanical stimuli were thought to be the sole mediators of the gastric phase [*70*]. In view of the foregoing there is ample evidence that there is, in addition, significant vagal release of gastrin. Thus the terms cephalic phase, gastric phase and intestinal phase of gastric acid secretion, or vagal, antral, intestinal mechanisms, should be discarded in favor of more specific terms. Nyhus et al. [*62*] recently suggested a new terminology for the stimulatory phases of gastric acid secretion as follows: (1) direct vagal, (2) vagal-antral, (3) local antral and (4) intestinal. The first of these four phases is purely neural, the second is neurohormonal and the last two are purely hormonal. Furthermore, a portion of the stimulatory effect of the vagi is active only if the antrum is present; similarly, a portion of the stimulatory effect of the antrum is active only if the vagi are present. As is apparent, the vagal-antral phase indicates the effect of vagal stimulation upon the antrum. The local antral phase encompasses both the local effect upon the antrum of chemical and mechanical factors. Finally, the intestinal phase remains, with a connotation similar to that previously understood.

The significance of vagal release of gastrin in human gastric physiology remains unclear. New operations are constantly being devised for the treatment of duodenal ulcer disease, operations devised to maintain a low recurrent ulcer rate as well as decrease the incidence of detrimental side effects such as malnutrition or dumping. Many of these operations are devised purposely to leave the antrum undisturbed. Because of the uncertain significance of vagal release of gastrin in man, careful consideration must be given to technical factors of antral exclusion and antral denervation. It will be most interesting to follow the long term results of these various antral-preserving operative technics [*71*].

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Influence of the Liver upon Gastric Secretion*

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THE liver is strategically located so that all substances absorbed or secreted into the portal venous system normally must traverse it before entering the general circulation. Thus it is in a position to excrete or metabolize them or allow them to pass unchanged. It is well established that the liver plays an important role in the metabolism of many compounds, among which are histamine and ammonium; products of digestion such as amino acids and glucose; and hormones such as serotonin, testosterone and desoxycorticosterone. During recent years there has been increased interest in the effects produced when portal blood bypasses the liver, due either to development of enhanced portal-systemic collateral circulation in cirrhosis or after the operation of portacaval shunt. This interest has extended to alterations in metabolism because of reduction in the ability of the liver to act in a normal fashion on materials in the portal venous blood. The present review deals with one aspect of this broad field, namely, changes in gastric secretion after portacaval shunts and their clinical implications.

ASSOCIATION OF ULCERS WITH CIRRHOSIS AND PORTACAVAL SHUNTS

The frequency with which gastroduodenal ulcer has been found in patients with cirrhosis of the liver varies widely. Undoubtedly this is partially due to variations in selection of patients to be studied, whether they be simply a group with proved cirrhosis, a group with cirrhosis and bleeding or a group with cirrhosis who have died. The problem of comparing the frequency of ulcers in cirrhotic and non-cirrhotic subjects is compounded by the difficulty of finding a valid control population without cirrhosis. However, most clinicians recognize with Morrow [*1*] that peptic ulcer is the source of upper gastrointestinal hemorrhage in many patients with portal hypertension.

Schnitker and Hass [*2*] found ulcers in 19.5 per cent of seventy-two patients with cirrhosis. Lipp and Lipsitz [*3*] found fifteen cases of peptic ulcer among 302 patients with portal cirrhosis, an incidence of 5 per cent. In postmortem studies on 130 cases of portal cirrhosis there was evidence of ulcer in fifteen, or 11.5 per cent, while among twenty-one cases of biliary cirrhosis there was evidence of ulcer in three, or 14.3 per cent. Among 1,000 autopsies on patients over thirty-five years of age who did not die of ulcer disease the incidence of ulcers was 6.6 per cent. In addition, they described four patients with portal cirrhosis who died of massive hemorrhage from ulcers, and another four who bled from ulcers and responded to medical therapy.

Palmer and Brick [*4*] found peptic ulcer in 2 per cent of 150 cirrhotic patients, fifty-nine of whom had a history of hemorrhage. Later Palmer [*5*] noted that in four of thirty-eight patients with esophageal varices who died of hemorrhage the bleeding came from erosive gastritis. Also gastric biopsies showed gastritis in ten of twenty-four patients with cirrhosis and esophageal varices.

Sullivan, Lienhard and Lukeman [*6*] reported three cases of coexisting active duodenal ulcer and cirrhosis with varices. Among ninety-six patients with portal cirrhosis or fatty infiltration of the liver they found four with peptic ulcer, an incidence of 4.3 per cent.

Fainer and Halsted [*7*] listed the source of upper alimentary tract bleeding in seventy-six patients with Laennec's cirrhosis. They found varices to be the source in 61.7 per cent, peptic ulcer in 18.4 per cent and gastric erosions in 5.3 per cent. In addition, they reviewed the reports of 1,278 consecutive autopsies and found cirrhosis in ninety-four. Peptic ulcer was present

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in 17 per cent of these ninety-four cirrhotic subjects while it was present in only 10.6 per cent of the other 1,184 cases in which there was no cirrhosis.

Swisher, Baker and Bennett [*8*] found peptic ulcers in fifty-eight patients, or 13.9 per cent, of 417 cases of Laennec's cirrhosis; sixteen of these patients were admitted because of bleeding from the ulcer.

Cohn [*9*] found a 6 per cent frequency of peptic ulceration among 583 patients with cirrhosis. Of sixty-eight cirrhotic subjects who died of gastrointestinal bleeding and were autopsied thirty-eight had bleeding from varices, twenty-three from no apparent anatomic cause, three from peptic ulcers, two from multiple erosions and two from esophagitis.

Davis [*10*] studied 100 consecutive autopsies on patients with cirrhosis of the liver, thirty-eight being Laennec's cirrhosis and twelve postnecrotic cirrhosis. He found chronic peptic ulcer in eight cases and acute ulcers in six additional cases.

Koide, Texter and Borden [*11*] found thirteen patients with peptic ulcer of 252 consecutive admissions with the diagnosis of cirrhosis, an incidence of 5.6 per cent. They summarized thirteen previous reports and made a calculation of 199 cases of ulcer among 2,672 patients with cirrhosis, an over-all incidence of 7.5 per cent.

Sporadic cases of peptic ulcers have been noted originating or becoming reactivated after portacaval shunt. However, the incidence of postshunt ulcer has not been high in most large series. Blakemore [*12*], in a one month to seven year follow-up of 130 patients who survived shunt, noted two late deaths after splenorenal shunts due to gastric ulcers. Ripstein [*13*] found no cases of postshunt ulcers in a one to five year follow-up of twenty-five cases. Jahnke et al. [*14*] found no cases in a one month to three year follow-up of thirty patients who underwent shunt. Child [*15*] saw one postoperative ulcer among thirty-seven patients subjected to shunting procedures. Linton [*16*] mentioned no ulcers developing in ninety-two patients who were followed one to nine years after shunt. Hallenbeck [*17*] followed forty patients who survived shunt for one to four years. Two of these who had end-to-side portacaval shunts died from bleeding ulcers. McDermott [*18*] described a patient who died a few months after portacaval shunt with bleeding from a huge duodenal ulcer. Ostrow et al. [*19*] studied a patient in whom a gastric ulcer developed within one month after splenorenal shunt.

The most suggestive report is that of Dubuque, Mulligan and Neville [*20*], who observed sixty patients up to eight years after end-to-side portacaval anastomosis and observed that gastrointestinal ulceration developed in 15 per cent. Of sixty-two portacaval shunts Clarke et al. [*21*] collected a group of five patients in whom ulcers developed within nine months after shunt. These ulcers appeared unusually resistant to medical therapy. Of these five patients one is well, one died two years after gastric resection for his ulcer because of recurrent drinking and liver failure and three died of bleeding from their ulcers.

In summary, the increased frequency of ulcers in patients with cirrhosis seems firmly established on the basis of the three autopsy studies mentioned [*3,7,10*]. The clinical studies vary widely in the incidence of ulcers found among cirrhotic subjects and suffer from lack of suitable control groups. However, it is evident that peptic ulcers occur in significant numbers in patients with cirrhosis, and probably more commonly than in the general hospital population of patients whose primary complaint is not ulcers. The frequency with which ulcers have been observed after portacaval shunt has also varied widely, and future follow-ups should pay close attention to this aspect of the problem. It is not possible to conclude at present that operative shunt enhances the ulcer tendency seen in the cirrhotic patients; but the time relations and severity of the ulcers in some shunt patients suggest that such may be the case.

LABORATORY STUDIES ON GASTRIC SECRETION AFTER SHUNT

Numerous mechanisms by which cirrhosis might predispose to ulcer formation have been suggested. Bockus [*22*] mentioned malnutrition, decreased amounts of biliary elements, central nervous system damage and inflammation and congestion of the gastric mucosa. The experimental evidence lies primarily in the demonstration that portal hypertension promotes ulcer formation and that procedures which divert portal blood around the liver increase gastric acid secretion and encourage ulcer formation.

Baronofsky and Wangensteen [*23*] ligated the splenic, left gastro-epiploic and left gastric veins in five dogs and found that large gastric ulcers developed in four and desquamation of the fundic

mucosa in the fifth after an average of 2.6 daily injections of 30 mg. of histamine in beeswax. In four dogs with portal veins occluded gradually by a cellophane ligature, large ulcers appeared in 2.3 days after injections were begun. Ulcers or erosions developed in eight of ten rabbits with splenic vein tie followed by histamine administration. In control animals no ulcers were seen. The authors noted a striking increase in weight of the stomachs of these animals with obstruction of the venous outflow from the stomach and edema of the mucosa and submucosa. They concluded that portal or splenic vein obstruction abets the ulcer diathesis. Their findings correlate with the observation of Lipp and Lipsitz [*3*] that in 113 autopsies on patients with congestive heart failure there was evidence of peptic ulcer in eleven or 9.7 per cent, while ninety-three (82 per cent) showed hyperemia, "mucoid gastritis" or petechial hemorrhages in the gastric mucous membrane. Thus portal hypertension may contribute to ulcer formation due to decreased local resistance. However, the findings of Baronofsky and Wangensteen may also be due to increased acid secretion associated with perihepatic shunts.

Lebedinskaja [*24*] first discovered in 1933 that secretion from gastric accessory pouches of dogs is increased after construction of an Eck fistula. She prepared two dogs with vagally innervated pouches and did feeding tests before and after making an Eck fistula. She found that the volume of juice secreted increased two to six times after shunt; that the duration of secretion was prolonged by two to three hours (from five hours to eight hours), that peptic activity fell and that acidity rose. These findings were confirmed in 1937 by Gerez and Weiss [*25*] in each of three Pavlov pouch dogs using a test meal of 300 gm. of meat.

Gregory [*26*] prepared dogs with gastric cannulas and denervated gastric accessory pouches. Secretory tests were made before and after gradual occlusion of the portal vein with cellophane tape not followed by liver atrophy. He again found that the operation was followed by an increase in volume and acid output from the pouch in response to feeding.

Gregory made several new and provocative observations. He found that the maximal secretory response to histamine gradually increased to about twice the preoperative level. The ability of the pouch to secrete in response to histamine may be increased by the presence of subliminal amounts of another endogenous stimulant or may be due to increase in the parietal cell mass of a pouch under constant excessive stimulation. Gregory also found in four dogs with vigorous appetites that the response of the pouch to meals began within fifteen minutes of offering food and that a considerable response followed sham feeding or teasing with food. Sham feeding for ten minutes or distention of the main stomach caused secretory response from both pouch and main stomach which lasted more than an hour if the gastric cannula was open. If the gastric cannula was closed, the pouch response soon fell to a low level. These experiments demonstrate that a stimulant of gastric secretion is released into the portal blood by vagal excitation as well as by feeding, that this stimulant is one whose action on a pouch is enhanced by hepatic bypass and that its release is inhibited by accumulation of acid in the stomach or duodenum. Although the site of origin of the stimulant is not localized, the inhibition of its action by acid in the stomach suggests that it may be gastrin.

An excellent study by Dubuque, Mulligan and Neville [*20*] measured the average twenty-four-hour output from canine Heidenhain pouches. In three dogs control laparotomy had no effect on secretion; in eight secretion increased from an average of 21.0 mEq. of free acid before to 63.9 mEq. after end-to-side portacaval anastomosis; in seven gradual portal vein occlusion with umbilical tapes increased acid output from 24.9 mEq. daily to 68.3 mEq., and after subsequent side-to-side portacaval anastomosis secretion remained at an average of 67.8 mEq. daily. They also gave 30 mg. of histamine in beeswax daily to eleven control dogs and twenty-seven dogs who had one of these operative procedures; five of the control dogs died in an average of twenty-three days; twenty-three of the dogs operated upon died, the average day of death being half that of the control animals. All but two of the dogs that died had perforated or bleeding ulcers. These findings agree with Baronofsky and Wangensteen [*23*] and prove that perihepatic shunts potentiate the ulcerogenic effects of prolonged histamine administration even in the absence of increased portal pressure and gastric mucosal congestion.

Similar striking increases in twenty-four-hour Heidenhain pouch secretion have been confirmed by others. Clarke et al. [*21*] measured secretion in nine dogs for twenty-six to forty-two days before and after portacaval transposition.

In this operation the portal vein and inferior vena cava are divided, the distal cut end of the portal vein is anastomosed to the proximal cut end of the vena cava and the distal vena cava is anastomosed to the proximal portal vein. Thus the portal blood is shunted around the liver but the liver still has a good venous blood supply. In contrast to an Eck fistula, this operation does not impair liver function [*27*]. All nine dogs showed increases in acid output after transposition, ranging from 92 to 850 per cent, with a mean of 344 per cent. Silen and Eiseman [*28*] found in six Heidenhain pouch dogs that the mean daily output of free acid on a regular diet was 19.8 mEq. before and 58.7 mEq. after portacaval transposition.

Hence it is firmly established that an increased secretion of acid occurs from gastric accessory pouches after feeding dogs who have undergone any one of several operations, their common denominator being a routing of portal blood around instead of through the liver. Since most of these studies were performed on Heidenhain pouches, which have little or no vagus innervation, and since Gregory's experiments [*26*] involved pouches which were carefully denervated of both vagal and sympathetic nerves, it is evident that innervation of the pouch is not a prerequisite for the phenomenon. This is further supported by the finding of Kohatsu et al. [*29*] that twenty-four-hour acid secretion was markedly increased after transposition in each of five dogs with vagus-denervated total stomach pouches. The question remains as to whether vagus innervation of the gastrointestinal tract exclusive of the indicator pouch is necessary. Gregory's demonstration that sham feeding will cause secretion from a denervated pouch after portal vein occlusion certainly shows that vagal excitation can play a role. However, in making a vagus-denervated total gastric pouch the vagi are divided at the lower esophagus, resulting in a total abdominal vagotomy. Hence the results obtained by Kohatsu et al. prove that the phenomenon can occur in the absence of vagal supply to the remainder of the gastrointestinal tract as well as to the pouch. As a result we must postulate a humoral gastric secretory stimulant which is released into the portal blood and is normally inactivated in the liver. It may be released by the vagal excitation of sham feeding but it is also very active after feeding when the vagi have been cut. In the presence of peripheral venous shunts it enters the general circulation in increased amounts and stimulates pouch secretion.

Is the gastric antrum the source of this secretagogue? We [*21*] found that antrum resection did not significantly reduce the hypersecretion following portacaval transposition in two dogs. Subsequently we have repeated the experiment in six additional dogs, each of which had a marked rise in mean twenty-four-hour acid secretion after transposition [*31*]. In four of these secretion was measured for thirty days after antrum resection with a Billroth I type reconstruction; in each case secretion fell after antrum resection but remained well above the pretransposition level. Two of the six dogs died on the sixth and seventh postoperative days from perforated ulcers. Since we have observed only one spontaneous ulcer in the main stomach and duodenum in over sixty-one dogs with transposition alone, their appearance in two of eight dogs with resected antrums is of interest and suggests that the antrum may be protecting against ulcer formation under these circumstances. Kohatsu et al. [*29*] likewise found increased secretion after transposition even though the antrum was functionless or nearly so, either because it had been transplanted to the abdominal wall (four dogs) or incorporated into a total stomach pouch (five dogs). In view of these findings Gregory's observation that acid in the stomach inhibits pouch secretion following sham feeding of dogs with portal vein occlusion [*26*] remains puzzling and unexplained. Either the stomach or duodenum is an important source of the secretory stimulant under these special conditions or acid in the stomach or duodenum is actually causing release of an inhibitory hormone.

Further evidence that the antrum is not an important source of this secretory substance was obtained by Clarke et al. [*30*] who studied the effect on Heidenhain pouch secretion of selective shunting of blood from various parts of the portal bed. In the dog the inferior mesenteric vein, draining the colon, joins the superior mesenteric vein, which drains the small bowel from mid-duodenum to ileocolic junction. The superior mesenteric vein unites with the splenic vein, which drains the upper duodenum, pancreas, stomach and spleen, to form the portal vein. The left gastric, entering the portal vein directly, also drains the stomach. When the superior mesenteric vein was anastomosed end-to-side to the vena cava, pouch secretion rose markedly in nine of ten dogs, an average increase

of 269 per cent. This showed that the stimulatory substance comes at least in part from the intestines distal to the mid-duodenum. A subsequent portacaval transposition was accomplished in six of these dogs, shunting the blood from the stomach, upper duodenum, pancreas and spleen around the liver, and redirecting the blood from the small bowel and colon through the liver. In each case acid output from the pouch fell promptly to near control levels. Under these conditions of long-term experiments on dogs who are eating normally the secretory stimulant originates predominantly in those portions of the gut drained by the superior and inferior mesenteric veins.

Subsequently we have carried out further experiments [*31*] utilizing inferior mesenteric vein to vena cava shunts. There was a profound increase in secretion in each of six dogs after the colonic venous blood alone was shunted around the liver in this manner. After portacaval transposition, by which all portal blood except that from the colon was shunted around the liver, these dogs had continued high rates of secretion. Hence the secretory stimulant originates in both the small bowel and colon. Although the colon is not ordinarily considered important in the intestinal phase of gastric secretion, it is a significant source of the secretagogue which becomes active after portacaval shunt.

Does the dog with a shunt continue to secrete abnormal amounts of acid when fasting? Clarke et al. [*21*] found that acid output in seven shunted dogs fell from a mean of 33.2 mEq. per twenty-four hours during feeding to a mean of 5.1 mEq. per twenty-four hours during a three-day fast. Silen and Eiseman [*28*] studied secretion during multiple one-day fasts in six dogs. Before transposition these dogs produced an average of 1.6 mEq. per twenty-four hours in the fasting state and after transposition an average of 8.7 mEq. Thus fasting secretion was distinctly elevated after transposition, even though it was much less than the average of 58.7 mEq. per twenty-four hours that these six dogs produced while eating a regular diet.

Does the bacterial content of the bowel affect the hypersecretion after shunt? Clarke et al. [*21*] gave neomycin orally in doses of 1.5 to 6 gm. per day to six dogs with portacaval transposition. No laxatives were given and the dogs continued on a standard diet. Acid secretion did not change significantly during three days on neomycin. Bacteria counts in the stool fell but sterilization was far from complete. Hence the effect of complete elimination of bacteria from the gut remains to be determined.

What is the effect of transposition on secretory response to various stimuli? Clarke et al. [*32*] found that the acid output after injection of 0.5 mg. of histamine diphosphate into the shoulder was greatly increased in three of four dogs. This was in accord with Gregory's finding [*26*] that the maximal secretory response to histamine approximately doubled after portal vein occlusion. Clarke et al. [*32*] noted that insulin induced hypoglycemia inhibited the elevated fasting secretion which follows transposition.

As far as feeding of the major dietary components is concerned, Clarke et al. [*32*] found in each of four dogs an increased secretory response after shunt to standard meals containing predominantly protein, carbohydrate and fat. Silen and Eiseman [*28*] found that the acid secretion after transposition increased 6.5 times in response to feeding glucose, 4.7 times after feeding lard and 4.2 times after feeding a protein hydrolysate (Aminosol®). In all cases the response to protein was much greater than to fat or carbohydrate whether before or after shunt. Silen and Eiseman also saw no effect on secretion after transposition in dogs given intravenous Aminosol whether infused into the foreleg or hindleg, the latter route directing the solution through the liver prior to its entry into the general circulation. They also noted no significant increase of secretion above fasting levels when dogs were fed alanine, histidine, lysine or tryptophane after transposition.

Is ammonium the stimulant which becomes active after shunt? We have observed [*31*] that intravenous ammonium salts cause a definite, though not profound, stimulation of gastric acid output when blood levels of around 400 μg. per 100 ml. are achieved. Silen and Eiseman [*28*] concluded that hyperammonemia is not the cause of postshunt hypersecretion. Although blood ammonium did rise shortly after feeding in dogs with shunts, the peak was in the range of only 150 μg. per 100 ml. and did not correlate with the acid secretion which came later; gastric instillation of ammonium citrate did cause a high rise in peripheral blood ammonium and concommitant pouch secretion, but the ammonium levels were far higher than occur under normal postcibal conditions; colectomy, presumably reducing the intestinal bacteria, did not alter the

elevated secretion in five transposed dogs. The fact that oral neomycin did not reduce secretion after transposition [*21*] is further evidence against ammonium playing a role.

Gerez and Weiss [*25*] commented that the elevation in volume and acidity and lowering of pepsin content of gastric juice after Eck fistula are similar to the changes after histamine administration. Histamine is a potent excitant of gastric secretion. Portal blood has a uniformly higher histamine content than peripheral hepatic or venous blood [*33*]. Urinary histamine levels are increased after feeding meat [*34,35*]. Silen and Eiseman [*28*] showed that systemic intravenous administration of histamine produced a far greater rise in pouch secretion than an intraportal infusion at the same rate and concentration. Irvine et al. [*36*] made similar findings and also noted an increased urinary histamine output when the infusion was systemic over that when it was intraportal.

Irvine et al. [*35,36*] have carried out extensive experiments supporting the role of histamine as an important gastric secretory excitant normally produced during digestion of meat by conversion of histidine by intestinal bacteria. In four men the normal increase in urinary histamine after a meat meal was inhibited by giving succinylsulfathiazole. Similar results occurred after giving 4 to 5 gm. of histidine orally, an amount comparable to that present in the meat. In three dogs the urinary histamine output in response to 5 gm. of histidine orally was likewise inhibited by previous sterilization of the gut with succinylsulfathiazole and chlortetracycline. Moreover they showed that these antibiotics do not prevent absorption of histamine from the gut of man or dog. They do inhibit formation of histamine when histidine is incubated with small bowel contents from dogs. At reasonable concentrations they do not prevent formation of histamine from histidine *in vitro* by tissue histamine decarboxylase from rabbit kidney. Thus the increased output of histamine in the urine after a meat meal is probably due to decarboxylation of histidine in the lumen of the bowel.

Irvine et al. [*36*] found that low doses of histamine placed in the upper jejunum of dogs with Heidenhain pouches caused no increase in basal acid secretion though there was a moderate increase in urinary histamine. Progressively larger doses of histamine caused increasingly large outputs of acid and urinary histamine. In two dogs a dose of intrajejunal histamine which did not stimulate pouch secretion before shunt caused marked consistent rises in secretion after side-to-side portacaval shunt. Furthermore, in three dogs the augmentation of acid output and urinary histamine levels during intraportal infusions was significantly lower than those during infusions into a peripheral vein at the same dose and rate, agreeing with the observations of Silen and Eiseman [*28*]. Also in two dogs the antihistaminase drug, aminoguanidine, potentiated the response of the Heidenhain pouch to histamine absorbed from the jejunum.

It may be concluded that a humoral excitant to gastric secretion is released into the portal blood from the enteric tract and is normally destroyed in the liver; that it originates predominately from the small bowel and colon; that its production is markedly increased after feeding, particularly of protein; that its secretory effects become quantitatively important when the portal blood bypasses the liver; and that in all probability one important such agent is histamine.

GASTRIC SECRETION IN PATIENTS WITH CIRRHOSIS AND PORTACAVAL SHUNT

Lebedinskaja [*24*] reviewed the literature prior to 1933 on changes in gastric secretion during cirrhosis or jaundice. Although some authors found an increased acidity of the gastric content under these conditions, others found it depressed, especially in advanced cases. Clarke, Costarella and Ward [*37*] found that mean hourly basal acid secretion was 1.39 mEq. in thirty control patients with no evidence of ulcer disease or cirrhosis, 0.88 mEq. in thirty patients with cirrhosis and 0.67 mEq. in eight patients after portacaval shunt. Also they found no significant difference in gastric secretion between the control and cirrhotic groups in response to a test meal of 250 ml. of 3.5 per cent sucrose in water as described by Hunt [*38*].

Recently Ostrow, Timmerman and Gray [*19*] published an excellent study on gastric secretion in "sick" and "healthy" patients with cirrhosis, cirrhosis and ulcer and cirrhosis and shunt. Uropepsin secretion was significantly decreased in forty-two patients with cirrhosis below control levels but was higher in eleven patients with cirrhosis and ulcers than in those without. Blood pepsinogen was lower in cirrhotic patients than in control subjects. Basal secretion of acid and pepsin was lower in cirrhotic patients than in

"healthy" control subjects but near control levels in patients with cirrhosis and ulcer; similar relations were found among these groups after histamine stimulation. Gastric output of acid and pepsin was significantly higher in eleven patients with cirrhosis after shunt than in a control group of twenty-nine patients with cirrhosis without shunts. Two patients were studied before and after shunt. One showed no increase in basal acid or pepsin secretion after portacaval shunt. The second had significant increases in basal and histamine stimulated acid and pepsin secretion one month after splenorenal shunt and at that time a gastric ulcer was seen on x-ray. However, on the average the secretion of eleven patients with cirrhosis and shunt was similar to that of ten with cirrhosis and ulcers and of nineteen "healthy" control subjects.

The available evidence, largely based on basal fasting and histamine tests, indicates that secretion is below normal in cirrhotic patients and is not usually above normal in cirrhotic patients after shunt. The animal work discussed earlier suggests that these tests may not be appropriate to bring out secretory abnormalities which may exist when part or all of the portal blood is deviated around the liver. Studies of gastric secretion in response to eating protein food or histamine, as suggested by Irvine et al. [*36*], hold more promise for showing hypersecretion after shunt in man.

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The Pathologic Physiology of Peptic Ulcer*

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THIS paper summarizes information on the ways in which patients with peptic ulcer differ physiologically from persons without ulcer. Particular attention is given to recent contributions to knowledge in this area. Such information is of the first importance for evaluating hypotheses about the etiology and pathogenesis of the disease and for developing a physiologically rational therapy. These topics are, however, beyond the scope of this presentation.

GASTRIC SECRETION

Acid. The mean concentration of acid in the gastric and proximal duodenal contents under basal conditions and after food is higher in patients with duodenal ulcer than in persons without ulcer [*1*]. That this is caused primarily by increased rate of secretion of acid, rather than by failure of acid to be neutralized, is supported by many observations showing that the mean rate of acid secretion under basal conditions, after food or after stimulation by drugs (histamine, caffeine, insulin) is higher in patients with duodenal ulcer than in those without this disease. (Table 1.) From such data on mean values the inference is frequently drawn that most patients with duodenal ulcer secrete an abnormally large amount of acid. Table 1 summarizes the incidence of abnormally high rates of secretion in patients with duodenal ulcer studied with various kinds of secretory tests. It is apparent that, although the mean rate of acid secretion is substantially higher in patients with duodenal ulcer, the percentage of such patients who secrete more than the upper limit of normal is, except in the instance of the caffeine test, 50 or less. It follows that only a minority of patients with duodenal ulcer will be distinguishable from persons without the disease on the basis of most of the standard secretory tests. The reason for the superiority of caffeine as a stimulus in segregating secretory responses of patients with duodenal ulcer is not known. It would appear to depend upon the prolonged response which these patients give to this stimulus [*3*]. The matter is worthy of further study for it may shed light on the mechanism of hypersecretion.

The mechanism of hypersecretion of acid in patients with duodenal ulcer is not fully established. The hypotheses which have been advanced include (1) impaired inhibition of secretion, (2) excessive stimuli for secretion, especially vagal, and (3) increased reactivity of the glands to stimulation.

Hunt [*8,9*] studied the inhibition of acid secretion which occurs when glucose or acid enters the duodenum. With glucose there was no difference between normal subjects and patients with duodenal ulcer, but with acid about a third of the patients with duodenal ulcer failed to show a normal degree of inhibition. However, since some patients with marked hypersecretion had normal inhibition by acid, it was concluded that a defect in the inhibitory mechanism is not a major cause of hypersecretion.

Because vagotomy usually abolishes the hypersecretion of patients with duodenal ulcer, it has been argued that the hypersecretion is caused by an excess of vagal stimuli [*10*]. There is a flaw in this reasoning [*11*]. Vagotomy not only abolishes secretion caused by vagal stimuli but also greatly decreases the response to other stimuli such as histamine [*12*]. Therefore, the reduction in secretion seen after vagotomy cannot be ascribed categorically to removal of excessive vagal stimuli for secretion. On the other hand, it is not possible, on the basis of the evidence available, to say that excessive vagal stimuli are not present in patients with duodenal ulcer. New methods are required to solve the problem. That salivary hypersecretion is correlated with gastric hypersecretion [*13*] is suggestive but far from conclusive evidence that parasympathetic overactivity may be present.

The most appealing hypothesis that has been offered to account for the hypersecretion of acid in patients with ulcer of the duodenum is that it

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TABLE 1

INCIDENCE OF HYPERSECRETION OF ACID AS MEASURED BY VARIOUS TESTS IN PATIENTS WITH DUODENAL ULCER

Stimulus	Units	Control Subjects			Patients with Duodenal Ulcer			
		Subjects (no.)	Mean	Upper Limit of Normal*	Subjects (no.)	Mean	Subjects Exceeding Upper Limit of Normal (%)	Reference
Basal	Free acid, mEq./hr.	137	1.4	2.8	238	2.8	42	2
Caffeine	Free acid at 90 min., mEq./L.	100	25	58	100	79	86	3
Caffeine	Free acid, mEq./90 min.	100	NA†	8.8	100	NA†	76	3
Caffeine	Free acid at 90 min., mEq./L.	82	14.7	43	48	55.1	65	4
Histamine	Free acid, mEq./hr.	24	11.8	18.7	20	15.2	30	5
Insulin	Free acid, mEq./hr.	24	16.5	23.6	20	17.1	25	5
Ewald meal	Free acid at 90 min., mEq./L.	100	31	55	100	41	30	3
Maximal histamine	Free acid, mEq./0.5 hr.	25	11.3	21	105	22.3	50	6

* Upper limit of normal was calculated by the method of Herrera [7] using 0.975 probability that more than 5 per cent of the control population was excluded.

† NA: not available.

results from the increased number of parietal cells which the gastric mucosa of these patients is known to have. Cox [*14*] found that both the area of the fundic gastric mucosa and its thickness were greater, on the average, in patients with duodenal ulcer than in persons without the disease. Corresponding to the increased volume of fundic mucosa was an increased number of parietal cells, with a mean of 1.8 billion in patients with duodenal ulcer and 1.0 billion in the control group.

In patients undergoing gastric resection, Card and Marks [*15*] correlated the decrease in acid secreted in response to maximal histamine stimulation with the number of parietal cells removed. They found a nearly linear relation between these two variables, with a slope of about 23 mEq./hour per billion parietal cells. This makes it possible to estimate the parietal cell mass from the secretory response to maximal stimulation with histamine in intact subjects. Such indirect studies [*6,16*] support the direct observations of Cox showing, in patients with duodenal ulcer, an increased mean secretory response to maximal stimulation with histamine and thus, by inference, an increased parietal cell population.

Hunt [*17*] and Hunt and Kay [*18*] found that the rate of acid secretion of control subjects and of patients with duodenal ulcer under basal conditions or in response to stimulation by test meals or drugs was proportional to their response to histamine. This held both for small and maximally stimulating doses of histamine. The fraction of maximal secretory response elicited by small doses of histamine was found to be the same in control subjects and patients with duodenal ulcer. These findings led to the conclusion that the hypersecretion of acid in patients with duodenal ulcer could be fully accounted for by the increased peripheral reactivity resulting from the increased parietal cell mass, making it unnecessary to postulate any abnormal secretory drive. Hunt and Kay [*18*] used the mean rates of secretion of the group to calculate the ratio of basal secretion to maximal secretion. Recently, Sircus [*19*] studied the basal and maximal secretion in 176 male patients with duodenal ulcer. He found that the percentage of maximal capacity to secrete represented by basal output increased as the basal rate of secretion increased. This suggests that high rates of basal secretion are associated with increased stimuli for secretion as well as with increased

TABLE II

INCIDENCE OF HYPERSECRETION OF PEPSIN AS MEASURED BY VARIOUS TESTS IN PATIENTS WITH DUODENAL ULCER

Test	Units	Control Subjects			Patients with Duodenal Ulcer			
		Subjects (no.)	Mean	Upper Limit of Normal*	Subjects (No.)	Mean	Subjects Exceeding Upper Limit of Normal (%)	Reference
Insulin	Units/hr.	24	7,639	11,000	20	12,599	45	5
Serum pepsinogen	Log units/ml.	4,150	2.64	2.84	203	2.88	55	25
Urinary pepsinogen	Units/hr.	38	54	77	51	80	45	26

* Upper limit of normal was calculated by the method of Herrera [7] using 0.975 probability that more than 5 per cent of the control population was excluded.

capacity to secrete. The subject invites further study, with attention to ratios of basal to maximal secretion in individual subjects rather than ratios of means of groups.

Why do patients with duodenal ulcer have larger than normal numbers of parietal cells? One possibility is that it is a genetically determined trait but there is no evidence for or against this supposition. Another possibility is that prolonged increased stimulation of secretion leads to hyperplasia of parietal cells. There is some evidence from studies in animals for the occurrence of such hyperplasia in response to prolonged increases in stimulation [*20*].

Sircus [*19*] found that both basal and maximal secretory rates increased with increasing length of history of symptoms in patients with duodenal ulcer. Hunt and Kay [*18*], however, found that such an increase occurred only in patients with pyloric stenosis.

The high secretory rates seen in patients with duodenal ulcer probably are present for years before the ulcer and its symptoms appear [*21*]. The rate of basal secretion does not change when the duodenal ulcer heals [*22*]. These findings indicate that the hypersecretion is not caused by the ulcer itself; they also suggest that the cyclic appearance and disappearance of the ulcer is related to factors other than variations in acid secretion.

In sharp contrast to patients with duodenal ulcer, those with gastric ulcer do not, in general, have abnormally elevated rates of acid secretion. There are, however, two categories of gastric ulcer to which this generalization does not apply, namely, prepyloric gastric ulcers and gastric ulcers occurring concurrently with duodenal ulcers. In both of these situations the mean rate of acid secretion is about the same as in patients with duodenal ulcer alone [*19,23,24*]. The remainder of patients with gastric ulcer secrete, on the average, less acid than persons without ulcer. Perhaps the same factor which causes depressed acid secretion also renders the mucosa more susceptible to ulceration.

Pepsin. In normal subjects and in patients with gastric or duodenal ulcer the rate of pepsin secretion is correlated with the rate of acid secretion, both under basal conditions and after stimulation by test meals or drugs [*17*]. Thus, just as with acid secretion, patients with duodenal ulcer show increased rates of pepsin secretion. (Table II.) The concentration of pepsinogen in blood serum and its rate of excretion in the urine are also increased in patients with duodenal ulcer. (Table II.) Serum and urinary pepsinogen do not fluctuate with short term changes in rate of gastric pepsin secretion produced by stimulation with food or drugs [*27*]. It is reasonable to assume that variations in pepsinogen levels in blood and urine reflect mainly variations in the gastric secretory capacity for pepsin secretion rather than changes in the extent to which this capacity is active.

Mucus. That mucus serves to protect the mucosa against digestion by acid and pepsin is an ancient and plausible notion which it is difficult either to prove or refute. The methods

available for measurement of the various kinds of mucinous substances in aspirated gastric juice have failed to reveal differences between persons with and without ulcer [*28,29*], except to show that increase in acid secretion is correlated with an increase in one class of mucoprotein. Presumably the layer of mucus which separates the mucosal cells from the contents in the lumen is of greatest importance in providing the alleged protection [*30*]. Study of the aspirated juices may not reflect changes at this critical site. Resolution of the matter awaits the development of suitable methods for study. The same may be said for other factors which are put under the necessarily vague, but probably crucially important, heading of tissue resistance to digestion. Until these factors are identified and means for measuring them are developed little can be said about them.

GASTRODUODENAL MOTILITY

The mean rate of gastric emptying of test meals of saline solution, glucose or acid is normal in patients with duodenal ulcer [*8,9*].

The frequency and amplitude of pressure waves during fasting in the stomach and duodenum of patients with gastric or duodenal ulcer do not differ from those of normal subjects [*31*]. There is some indication that pressure waves in the stomach and duodenum may be increased in frequency and amplitude during the occurrence of pain from peptic ulcer [*31,32*]. There is no evidence for the existence of a derangement of gastroduodenal motor activity which might act as a causative factor in peptic ulceration.

BLOOD GROUP

Observations in many countries have established that persons who possess blood group O have a higher incidence of peptic ulcer than those with other blood groups. Although some of the individual series which have been reported fail to show a higher than expected incidence of blood group O in patients with peptic ulcer, when all reported series are combined and examined by suitable statistical methods the association between blood group O and peptic ulcer, both gastric and duodenal, is fully supported [*33*]. The combined results from all centers show that the risk of having a duodenal ulcer among persons with blood group O is approximately 1.4 times the risk among persons with groups A, B or AB. Similarly, the risk of O subjects having gastric ulcer is 1.2 times that of persons having the other three blood groups.

Some have claimed that the association between blood group and gastric ulcer is valid only for ulcers in certain locations in the stomach. Several large recent studies [*34,35*] have, however, shown that there is no evidence of an association between blood groups and the site of the ulcer.

Several groups [*35,36*] have noted that the association with blood group O is more marked for stomal ulcer than for duodenal ulcer. In patients with duodenal ulcer no significant correlation was found between blood group and acid output in response to maximal stimulation with histamine [*36*].

Another genetic factor which may be involved in the etiology of peptic ulcer is the secretor status. This trait is determined by a single pair of allelic genes independent of those for ABO groups. About 75 per cent of persons secrete ABH substances in saliva and gastric juice (A and H secreted in group A secretors, B and H in group B secretors, A, B and H in group AB secretors, and H in group O secretors). Clarke and co-workers [*37*] found a clear association between ABH non-secretion and duodenal ulcers. The excess incidence of non-secretors was found with equal frequency in patients with all four ABO blood groups.

The liability to duodenal ulceration from being simultaneously O and non-secretor is at least additive. Thus Clarke and co-workers [*37*] calculated that O non-secretors were 2.49 times more liable; A, B and AB non-secretors 1.60 times more liable; and O secretors 1.35 times more liable to develop duodenal ulcer than are A, B and AB secretors.

Using fluorescent antibodies, Glynn and co-workers [*38*] demonstrated that A substance is present in the surface epithelial cells of the stomach and duodenum in A secretors but not in non-secretors.

All of these observations invite the speculation that the presence of certain blood group substances in the secretions and cells of the stomach and duodenum in some way protect against duodenal ulceration. Non-secretors of ABH usually secrete much more of another blood group substance, Lewis, than do ABH secretors. The total amount of all blood group substances, as estimated from the fucose content of saliva, has been shown to be the same in secretors and non-secretors and in subjects with and without

duodenal ulcer [*39*]. This suggests that the association between blood groups and secretor status and duodenal ulcer may be related to differences in the properties of A, B, H and Lewis group-specific substances.

MISCELLANEOUS OBSERVATIONS

The secretory response of the pancreas to intravenously administered secretin is normal in patients with duodenal ulcer [*40*].

Certain rare forms of peptic ulcer disease are clearly associated with endocrinopathies [*41*]. This has led to an interest in endocrine function, particularly adrenocortical, in the usual patient with ulcer. There is no evidence for increased adrenocortical activity in patients with active or inactive peptic ulcers [*42*].

CONCLUDING REMARKS

Although some patients with duodenal ulcer secrete abnormally large amounts of acid and pepsin, many secrete normal amounts. Patients with prepyloric gastric ulcer have secretory patterns similar to those with duodenal ulcer. Ulcer of the body of the stomach is associated with decreased acid secretion. The secretory levels of these various groups are to a large extent determined by the amount of glandular tissue in the stomach; alterations in the amount of stimulation playing upon the glands may contribute but have not as yet been clearly established. Because many instances of gastroduodenal ulceration cannot be ascribed to hypersecretion of acid-pepsin, a decrease in resistance of the mucosa to ulceration is postulated but means of measuring this factor are, as yet, lacking.

No characteristic alterations in gastroduodenal motor activity exist in patients with peptic ulcer, except perhaps during periods of pain.

The demonstration that persons with blood group O and persons who are non-secretors of ABH substances are more likely to have duodenal ulcer has established the existence of a genetic factor in this disease and has opened new avenues for research on its pathogenesis.

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Geographical and Environmental Aspect of Peptic Ulcer*

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THE world-wide importance of peptic ulcer disease has been pointed up in surveys carried out by the World Health Organization. In most of the countries covered by their studies "ulcers of the stomach and duodenum are responsible for more deaths than cirrhosis of the liver, bronchitis, non-epidemic influenza and other common infectious diseases" [*1*]. The apparent major differences in distribution of peptic ulcer disease over the globe [*2*] however, have led many workers to the opinion that geographical and environmental factors are etiologically important. Just how important has not been established for want of good epidemiologic data. The design of most available studies of geographical, social and occupational distribution is not sufficiently sophisticated to give definitive answers. Moreover, the attempts to gather data on either the prevalence or incidence of the disease have been seriously hampered by the fact that peptic ulcer is not a reportable disease, that many persons with peptic ulcer do not consult a physician for their symptoms, and when they do, criteria for diagnosis are not uniform. Data from necropsy records [*3–5*], questionnaires to physicians [*6*], various types of population surveys [*7–9*] and insurance company statistics [*10*] are available, mainly on selected populations. Some of the studies have been prospective; more of them retrospective. While the findings are interesting and provocative, it is not possible to generalize them to other populations or to the general population.

Geographical Distribution. The work of many investigators has been focused on determining the difference in incidence between gastric and duodenal ulcers, or between males and females. In most areas of the world, duodenal ulcers have predominated in clinical studies, and males have been the chief victims [*11,12*]. In a fishing district in the northern part of Norway, however, during the years 1941–1944, Schanke [*13*] found gastric ulcers three times more common than duodenal ulcers. Gastric ulcer predominated 20 to 1 in the study of Garrido-Klinge and Pena [*14*] of a hospital population in the Peruvian Andes. Among the interesting investigations of special populations is that of Knutsen and Selvaag [*7*], who made a study on the incidence of peptic ulcer disease in the town of Drammen, Norway (population, 25,830). This study was unique because during World War II patients who had peptic ulcers had to turn in a card for special rations and had to have roentgenographic verification of their disease. The over-all ulcer rate was 2.08 per cent in the total population and 2.45 per cent for the population over fifteen years of age.

Another outstanding report was that of Pulvertaft [*8*], who gathered data on all new peptic ulcers developing in the residents of the City of York, England, and in the surrounding country districts in the six years 1952–1957. Both hospital and private practice was covered. Ulcers were judged to be present when they caused acute hemorrhage or perforation, when they were found at necropsy, gastroscopy, at operation or when they were demonstrated roentgenographically. As the size of the total population at risk was known it was possible to estimate the frequency with which ulcers occurred in this population. There were 105,371 inhabitants of the City of York, and 33,335 people in the country area. In the six years, 1,132 ulcers were found, 823 in men and 309 in women. The over-all incidence expressed as the mean annual incidence rates per 1,000, aged fifteen years and over, were as follows: duodenal ulcer, 2.15 in men and 0.62 in women; gastric ulcer, 0.53 in men and 0.31 in women. Analyzed on a town and country basis the incidence of gastric and duodenal ulcers in both sexes was

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found to be higher in the town than in the country. Only among the men, however, were the town and country differences statistically significant. The findings further suggested that age is a factor in the incidence of gastric ulcers in males, and in both duodenal and gastric ulcers in females; it is, however, a less significant factor in duodenal ulcers in males.

The number of patients with acute perforated peptic ulcers in the years 1952–1953 from this study were compared with figures for the same years from Glasgow as reported by Jamieson [*9*]. The mean annual rates per 100,000 population in Glasgow were 32.6 in males and 3.2 in females as compared with 26.6 in males and 2.8 in females from York. It would appear that acute perforations, particularly in males, are more common in Glasgow than in York. The incidence of peptic ulcers found in York was also compared with the frequency of incidental chronic active ulcers found at necropsy in patients from the town of Leeds [*15*]. On this basis, the incidence of duodenal ulcers in York and in Leeds was quite comparable, but gastric ulcers seemed appreciably less common in York. Computing the annual risk of duodenal ulcers developing in males living in the city of York the risk was 2.58 per 1,000, while it was 2.07 per 1,000 for males in London [*16*]. The only really safe inference from these studies and others from other parts of the world is that the incidence of ulcers, both gastric and duodenal, varies greatly from place to place and from time to time in the same place [*2,4,5,6,10,17*]. No place or time seems to be altogether spared. The estimated incidence of peptic ulcers, depending on the population and method of collecting data, varies from as low as less than half of 1 per cent to as high as 20 per cent [*1,11,12*].

Climatic and Seasonal Variations. Hippocrates once said "Whoever wishes to pursue properly the science of medicine must proceed thus: First, he ought to consider what effects each season of the year can produce; for the seasons are not alike, but differ widely both in themselves and at their changes. For with the season men's diseases, like their digestive organs, suffer change." In both animals and man it has been shown that the volume and acidity of gastric juice is higher in autumn and spring than in the other seasons [*18,19*]. In temperate zones of the world the incidence and severity of the symptoms of peptic ulcer in man are generally believed to be greater in fall and spring, as shown in Table 1. However, surveys from various parts of the world report a peak incidence in every month of the year except July. The data verifying these seasonal variations in some studies is sparse and in others it is not given. It is of interest that no seasonal variations were seen in Mexico [*20*] and Brazil [*21*]. It has been suggested that the constant mild nature of the climate may explain the lack of seasonal variation in the incidence of ulcers, although in neither country is the climate really uniform. Furthermore, in this connection it is notable that no marked seasonal variation has been reported from Switzerland [*22*]. The highest incidence of recurrence or new cases of peptic ulceration has been reported to occur in northern Norway from January through April [*13*] and in western Norway from November through January [*23*]. In contrast the highest incidence in Australia occurs in May and June [*24*]. While the information concerning perforations from gastroduodenal ulcer in the United States is at variance (Table 1), it appears that perforations most frequently occur in December both in London [*35*] and West Scotland [*9*]. In contrast, in North-East Scotland perforations occur more frequently in the summer, and the sharp rise in incidence during December which is found in Glasgow does not occur [*36*]. Interesting short-term variations in the frequency with which perforations occur in Scotland have been demonstrated [*9*]. Perforations occurred most frequently on Friday and Saturday, while they were uncommon on Sundays and Mondays. During a twenty-four-hour period they occurred more frequently towards the end of the morning and the end of the afternoon.

The periodic variations have been related to seasonal effects on the patient's cardiovascular system and in the chemical composition of his blood [*37*]. Others have thought they were correlated with temperature or barometric pressure changes [*19,25,28*]; however, there is evidence, at least in Canada, that this is not the case [*32*]. In some series there has been good correlation of peak seasonal occurrence with infections of the upper respiratory tract [*9,25,26*]. The gathering of all these data has been a laborious process but even greater than the difficulty of gathering epidemiologic data in peptic ulcer is the difficulty of drawing inferences from whatever differences can be established as to prevalence or incidence from place to place or time to time. The data have been used to

TABLE 1

SEASONAL VARIATIONS IN PEPTIC ULCER DISEASE AND ITS COMPLICATIONS REPORTED IN NORTH AND SOUTH AMERICA

Authority	Location	Type of Ulcer	Time of Increased Incidence
		Recurrences or Appearance of New Cases	
Bolt [25]	Michigan	Duodenal	May, June, September, October
Texter [25]	Chicago	Gastroduodenal	April, October
Texter [25]	North Carolina	Gastroduodenal	December (Christmas)
Einhorn [26]	New York	Gastroduodenal	September, May
Flood [27]	New York	Duodenal	March, November
de le Vaga et al. [20]	Mexico	Gastroduodenal	None
Siffert [27]	Brazil	Gastroduodenal	None
		Hemorrhage	
Boles and Westerman [28]	Pennsylvania 1949–1953	Duodenal	January, February, March, October, November, December
Boles and Westerman [28]	Pennsylvania 1949–1953	Gastric	January, February, April, May, June
Bandler and Desjardins [29]	Pennsylvania 1953–1958	Duodenal	January, February, March, October, November, December (Peak: October and March)
Flood [27]	New York	Duodenal	April, October
Rosenak et al. [30]	Indiana	Gastroduodenal	February, August, September, October
Boles et al. [31]	Massachusetts	Duodenal	Slight increase in January
Bingham [32]	Canada	Duodenal	November, December
		Perforation	
Magladry et al. [33]	California	Gastric	Winter
Magladry et al. [33]	California	Duodenal	None
Shawan [34]	Michigan	Gastroduodenal	Summer

support a variety of conflicting theses. Various theories have implicated meteorologic variations, dietary habits, traumatic stresses and emotionally stressful situations.

Animal Studies. Experimental ulcers have been produced in white rats placed in a cage and subjected to intermittent stimulation with a light and to vigorous mechanical motion for twenty-three of twenty-four hours [38]. More moderate motion of the same type failed to induce ulcers. Experimental ulcers have also been induced by placing animals in unaccustomed restraints. The efficacy of this method has been shown to vary with the species of animals used. In one series, gastric ulceration was produced in 92 per cent of mice, 86 per cent of rats, 46 per cent of guinea pigs and 4 per cent of hamsters [39]. No gastric ulcers were induced in rabbits or monkeys by this technic. It was further shown that the incidence of gastric ulcers produced by the restraint methods in rats was increased if the animals were deprived of food or if relatively young rats were used. Repeated periods of restraint also increased the incidence and severity of the gastric ulcers. Ader et al. [40] found that twenty hours of immobilization plus deprivation of food and water induced more gastric erosions in Wistar rats than in Sprague-Dawley or Long-Evans rats. In addition, whereas there were no strain differences in susceptibility among male rats, Wistar female rats had a greater number of gastric erosions per animal than did Sprague-Dawley female rats. Thus it would appear that the occurrence of experimental ulcers in animals depends not only on the degree of environmental stress but also on the age, sex, strain and species. No direct correlations can be drawn from these studies as to the etiology of

peptic ulcer disease in man, but they do illustrate a multiplicity of factors involved and the difficulties of separating them.

Occupational Hazards. The association of various occupations with an increased incidence of peptic ulcers has received a changing emphasis from the nineteenth to the twentieth century. Early studies, stressing the role of mechanical factors and gastric irritants, implied that cooks and bootmakers were the most frequent sufferers from gastric ulcer. During the twentieth century there has been little agreement as to which occupations predispose or contribute to peptic ulcer disease. Doll, Jones and Buckatzsch [*16*] summarized the majority of the investigations prior to 1951 concerning occupational factors. Many of the studies had emphasized the likelihood of transport workers having ulcers. In addition, it was implied that rural workers, clerks and sedentary workers were less likely to have ulcers than industrial workers or laborers. When the statistical basis for these conclusions were reviewed they did not seem justified in many instances. Doll, Jones and Buckatzsch [*16*] attempted to circumvent the errors of previous studies and to better define the possible influence of occupation. They undertook a large-scale survey utilizing personal interviews and medical examinations of workers in different occupational groups. As they point out, since the majority of the persons they investigated were from London, their findings cannot be taken to represent those for all of England. They studied the records of 6,047 men and women, with 1,284 of them having medical examinations. They found evidence of 334 peptic ulcers among the group. A disproportionately large number of duodenal ulcers were found among foremen and business executives. In contrast the incidence of ulcer disease among agricultural workers was significantly low. They could not verify the previous reports showing a high incidence among transport workers. Pulvertaft [*8*], in his investigation of York and the surrounding country districts, had somewhat different findings. Gastric ulcers were significantly more common in the semiskilled and unskilled workers than in skilled artisans or professional and semiprofessional groups. A comparison of mean annual incidence rates of duodenal ulcer for men thirty-five years old and over for agricultural workers and for all other occupations combined was similar in his investigation. Weir's study [*17*] in North-East Scotland suggested that the frequency of perforations in that area was highest among heavy and unskilled workers and infrequent among non-manual workers.

Alsted's study in Denmark [*6*] stressed the importance of taking age into account in studies of occupational factors. He found a high incidence of peptic ulcers in older executive office and administrative personnel, in older lawyers and doctors. The incidence rate was also high among older motor drivers and extremely high in a collective group comprising traffic and transport personnel over sixty-five years of age. Schanke [*13*] in his investigation of a fishing district in the northern part of Norway found peptic ulcers more prevalent in the fishermen in this area than in any other occupational group. It may not be proper to lump all persons in one occupation together as shown by Dalhamn's study on Swedish sea pilots [*41*]. He found that the morbidity due to peptic ulceration was highest among those pilots who were at the stations with the greatest burden of work.

Adaptive Problems and Characteristics of the Individual. Although efforts to associate peptic ulcer with occupational hazard have not yielded a consensus among workers, there does seem to be general agreement that there is a higher incidence of peptic ulcer in the cities than in the country in most parts of the world, and that persons whose work involves executive responsibilities, are more prone to ulcer than wage earners. This finding is particularly interesting in view of studies on monkeys made by the group at Walter Reed Hospital [*42,43*]. In their first group of experiments, nineteen monkeys were gently restrained in chairs, with freedom of all their limbs. They were subjected to various combinations of behavioral conditioning procedures. Eleven of the original nineteen animals died or became moribund and had to be sacrificed after two to seventeen weeks of the experiments. In many of these animals hemorrhage and/or erosion of the stomach or duodenum developed. In a second group of experiments the animals were paired and placed side by side in restraining chairs. The chair of one of the monkeys was provided with a lever which, if pulled at the right time, would prevent both animals from receiving an electric shock. The second monkey had only a dummy lever. The animals were then subjected to electric shock for periods of six hours alternating with rest periods. The first monkey, which the investigators referred to as the "executive"

monkey, rapidly learned that he could prevent the electric shock to both animals by pulling his lever at the correct time. The second, or passive monkey, learning that his lever was a dummy, soon lost interest in it. Duodenal ulcer, frequently with death by perforation, occurred in each "executive" monkey whether or not he was isolated from his "passive" partner. However, ulcers did not develop in the passive monkey. It was further observed that the peak of gastric acid secretion in the "executive" monkeys was reached a few hours after each period of stimulation while the animal was presumably resting.

In man it is well known that the symptoms of peptic ulcer begin after an emotional stress [*44*]. In one study of American soldiers the symptoms of peptic ulcer had occurred in several on the day they appeared before their local board [*45*]. In others, symptoms were first noted after the first meal was eaten at the reception center. After discharge from the Army was assured, there was a remarkable subsidence of previously refractory symptoms in some soldiers. In others symptoms recurred when they were told to return to duty. Perforated peptic ulcers have been noted to occur in great numbers during periods of heavy air raids [*35*]. It has been hypothesized that many patients in whom peptic ulceration develops have a deep dependence on a feeling of personal security within a group [*46*]. This may account for the fact that the increased incidence of ulcer disease during World War II in Germany was not among the frontline troops, but among the home services and the services behind the lines [*47*]. Also that the incidence rate of ulcer disease decreased in concentration camps, but increased after liberation of the prisoners [*48*].

The confusion surrounding attempts to relate peptic ulcer to psychological conflicts derives in part from a rigid and unrealistic concept of cause. Recently, however, medical men are discovering again that the best view of the cause of disease is that of the algebraic equation in which many relevant factors contribute for and against. Thus the inherent characteristics of the individual person must be considered as well as any forces which may be brought to bear upon him.

The Secretion of Acid. Apart from the lesion in the duodenal mucosa, the only bodily change which is known uniformly to accompany peptic ulcer disease is an excessive production of gastric hydrochloric acid and pepsin—excessive because it is sustained rather than intermittent as at meal time. If hypersecretion of hydrochloric acid is an important element in the mechanism of ulceration, those factors associated with an increase would be expected to weigh heavily in the balance. Thus the seasonal predominance of the symptoms of ulcers in fall and spring, in some persons at least, would appear to be related to the demonstrated higher acid secretion at those times. It follows also, that the well documented increase in acid secretion during periods of emotional conflict characterized by concern or unconscious frustration and hostility must assume some importance [*49–51*]. It is of special interest that under some circumstances symbolic stimuli may exert a more powerful secretogogue effect than chemical agents such as histamine or insulin. In the experiments of Janowitz [*52*] good appetite was accompanied by a more profuse secretion of acid than was the injection of histamine or insulin. Similarly, a "stress interview" covering personal conflicts evoked an acid response when repeated injections of histamine had failed. Both good appetite and feelings of resentment have been shown to be accompanied by similar behavior of the gastric glands. This intriguing fact has provoked a welter of speculation in the medical literature. The most widely held idea is that the brain circuits subserving appetite are closely allied to those which mediate the need for psychologic sustenance or the figurative wish to devour. Such reasoning has given rise to what might be called the biological principle—*as if* [*53*]. It emphasized the fact that bodily structures may react not only to tangible stimuli but also often *in anticipation* of the stimulus. Thus heart rate accelerates before a race and saliva and gastric juice flow before a meal. It is equally well established that heart rate may accelerate during anxiety without any conscious anticipation of running. Saliva may flow under stress or gastric acid may be secreted in greatly increased amounts in the person who is frustrated and resentful. Thus, although there is no conscious wish to devour, the glands of the stomach behave *as if* there were. It may be more than coincidence, therefore, that those who have studied patients with peptic ulcer from a psychologic standpoint find them a lean, hungry, competitive lot.

There are not enough clean-cut systematic data gathered in a sufficiently uniform way to answer most of our questions about the relation-

ship of man's environment to the pathogenesis of peptic ulcer. In the search, however, it has seemed increasingly likely that the individual's *inherent nature* and the *way* in which he meets forces in his environment are at least as important as the characteristics of the forces themselves in determining health or disease.

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Endocrine Tumors and Peptic Ulcer*

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WHAT causes the stomach to join the endocrine glands in a conspiracy against itself? Although the answer is coming into better focus, it is still not clear precisely how and why peptic ulceration is produced, often in association with excessive amounts of gastric acid. The tendency to see an "endocrine relationship" in so many diseases in present day medicine and surgery makes an evaluation of their importance in the ulcer problem difficult. An attempt has been made to bring together some of the evidence linking one or more of the endocrine glands to the etiology of peptic ulcer.

Parathyroid Tumors. The parathyroid adenomas were the first endocrine gland tumors whose hyperfunction was associated with a significantly increased incidence of peptic ulceration [*32*]. In 1946, Rogers called attention to the marked similarity between the gastrointestinal symptoms in hyperparathyroidism and peptic ulcer. He hypothesized that because of this similarity of symptoms many cases of hyperparathyroidism were being overlooked. Over the next few years reports from the leading medical centers in this country of their experiences with hyperparathyroidism appeared in the literature. The over-all incidence of peptic ulcer proved to be about 13 per cent [*17,23,36*]. (Table 1.)

The peptic ulcers associated with parathyroid tumors have usually occurred in the duodenum and, although gastric hypersecretion has not been a consistent finding, they have resisted medical therapy. Such ulcers have responded promptly and permanently to excision of the offending parathyroid adenoma [*37*]. However, two cases of hyperparathyroidism were reported in which the ulcer diathesis persisted after removal of the parathyroid adenomas. Eiseman et al. [*10*] and Poth, Chvojka and Singleton [*5*] treated patients with parathyroid adenomas associated with a non-beta islet cell adenoma of the pancreas. In both of these cases removal of the parathyroid adenoma, although reversing the blood chemical values to normal, did not alter the ulcer diathesis until total gastrectomy was performed. These polyglandular cases support the thesis that the pancreatic non-beta islet cell tumors play the dominant role in the etiology of associated intractable ulcer.

TABLE 1
INCIDENCE OF PEPTIC ULCER

	Per cent
Ulcerogenic tumors	
Pituitary	1
Adrenal	1
Parathyroid	13
Pancreatic islets	
Beta cell	1
Non-beta cell	85

In man and animals, experiments on the effect of parathormone on ulcer production and gastric acid secretion have not been particularly rewarding. Heuper [*19*] has produced areas of edema and hemorrhage in the stomach and duodenum in animals by injections of large doses of parathormone. Microscopically, calcification of the glandular epithelium and thrombosis of the smaller submucosal vessels were the most prominent changes. He proposed that dehydration together with decreased cardiovascular and vasomotor tone and an increase in blood coagulability lead to necrosis of the gastric glands with ulceration and subsequent calcification. Donegan and Spiro [*8*] recently studied the gastric secretory response in man to short-term injections of massive doses of parathormone and to chronic parathyroid hyperfunction both before and after removal of the tumor. There was no significant change. Hypercalcemia induced by the intravenous administration of calcium lactate resulted in a modest rise in acid output.

Although excess parathormone does not alter

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gastric secretion, a deficiency of this hormone will profoundly reduce gastric secretion.

Apparently, the principal function of this hormone is to maintain the calcium level above 7 mg. per cent. Below this level, normal gastric secretion does not take place [*20*].

The surgical management of patients with ulcer and hyperparathyroidism is directed toward removal of the hyperfunctioning parathyroid tissue. All four glands must be explored, and on rare occasions a fifth parathyroid has been found in the thymus gland. In the presence of an obvious adenoma, simple excision of the tumor will suffice. According to Cope [*6*], if hyperplasia is found, at least three parathyroids should be completely removed, with subtotal resection of the fourth if it is enlarged. The surgeon must be familiar with all the anatomic variations and locations of the parathyroids, both in the neck as well as in the mediastinum.

Adrenal Glands. Many clinical and experimental studies have been conducted to evaluate the association between the adrenals and ulcer, but the results have been conflicting. While overactivity of the adrenal cortex has long been suspected of playing a role in the etiology of ulcer, there is little evidence linking any type of adrenal tumor with an increased incidence of peptic ulceration. Indeed, ulcer has been reported in only 1 per cent of patients with Cushing's syndrome secondary to hyperfunctioning tumors of the adrenal cortex [*16*]. Furthermore, measurements of steroid excretion have been reported to be in the low normal range in cases of the polyglandular endocrine syndrome with coexistent adrenal tumors and peptic ulcer. The cortical tumors, either adenomas or carcinomas, have not been differentiated as to their respective ulcerogenic potential. Since there is no proved relationship between peptic ulcer and adrenal tumors, they should be treated independently. When they coexist, total excision of the adrenal tumor ordinarily would have priority [*11*].

Total excision of tumor tissue is the recommended treatment for adrenal tumors which are functional and coexistent with peptic ulcer. Temporary steroid replacement therapy will be required until the remaining atrophied adrenal has resumed full function.

The association of peptic ulcer with adrenal medullary tumors is infrequent, the incidence being estimated at less than 1 per cent [*22*].

Pituitary Tumors. The pituitary gland has little direct effect on gastric acid secretion and peptic ulceration. Wilson et al. [*45*] found the incidence of ulcer to be 1 per cent in a review of 512 patients with acromegaly. The frequency of ulcer was the same in basophilic tumors whether or not adrenal cortical hyperfunction was also present [*16,26,40*]. There is no evidence that chromophobic tumors cause gastric hypersecretion or an increased incidence of ulcer [*12*].

Hypophysectomy in experimental animals has been found to affect gastric secretion profoundly and to reduce the parietal cell mass in the stomach by 50 per cent. The administration of adrenal cortical hormones is only partly effective in returning these cells to normal. This implies that the pituitary gland is directly concerned with normal gastric secretion, but the mechanism is unknown [*1*].

Pancreas. Ulcerogenic tumors of the pancreas were first noted in 1955 [*47*]. At that time a diagnostic triad was suggested, consisting of (1) excessive gastric acid secretion, (2) fulminating, often atypically located peptic ulceration, and (3) non-insulin producing islet cell tumors of the pancreas. In patients who have not had previous gastric surgery, the tendency toward atypical location of the ulceration in the distal duodenum or, more specifically, in the upper part of the jejunum has been practically pathognomonic of ulcerogenic tumor. Also characteristic of the disease is the early return of marked gastric hypersecretion and fulminating ulcer following radical gastric surgery, despite intensive medical therapy (including radiation of the stomach), and—more rarely—the protective influence of pregnancy [*39,50*].

Since the original description of the ulcerogenic tumor syndrome in 1955, intractable diarrhea rather than intractable ulcer has been recognized as occurring in a small per cent of patients with non-beta islet cell tumors. Thirteen of the eighty patients with these tumors have had significant diarrhea [*4*]. The diarrhea often precedes the peptic ulcers by months or years. Most frequently it is of a watery nature, occasionally it is sprue-like, but always intractable to the usual forms of treatment. These patients become dehydrated and have marked potassium loss in the stool. Vacuolar nephropathy secondary to hypopotassemia has always been found in the fatal cases [*42*].

Six patients have not manifested peptic ulceration. One such patient was dramatically cured of his diarrhea by resection of a solitary

non-beta islet cell tumor [*2*]. When acid levels have been studied, these patients have had marked gastric hypersecretion, which may overcome the neutralizing power of the basic pancreatic exocrine secretion [*38*]. Not only would the pancreatic enzymes be inactivated, but the acid would also cause marked irritation of the small bowel mucosa, with hypermotility.

The ulcerogenic stimulus is indeed a powerful one but its mode of action is unknown. Recently, experiments have been carried out which promise to shed light on the nature of this hormone.

The original report on ulcerogenic tumors suggested that glucagon might be the humoral substance responsible for this syndrome [*47*]. This hypothesis has not been borne out, since both human and animal experiments clearly show that glucagon depresses both gastric secretion and motility [*9,31*]. Serotonin was also thought to be a possible etiologic agent because microscopically many of the tumors resembled carcinoid tumors. However, serotonin has been ineffective in stimulating gastric secretion, and the breakdown products of serotonin in the urine have not been found to be increased in this disease [*18,35*].

The first experiments involving the actual use of tumor tissue were carried out by three groups of investigators. A potent gastric stimulant has been demonstrated in two separate ulcerogenic pancreatic adenomas.

The methods of tumor extraction by the two groups have differed. Osborne, Brown and Le Compte [*25*] received a 2.2 gm. sample of tumor tissue which had been kept frozen for two years. The tumor was divided into two equal parts, homogenated, and triturated into saline solution. Each sample was dialyzed for twenty-four or forty-eight hours against saline solution. Both the saline extracts and its dialysate were administered intravenously to two dogs with Heidenhain pouches. The dialysate only moderately lowered the pH. The saline extract lowered the pH from neutral to 1.6 within the first hour.

These observations were controlled by similar preparations of normal human liver and pancreas, which were without effect. Blood sugar levels were not altered by the injections. Chemical analysis of the injected materials showed only traces of histamine. Osborne characterized the active principle as water-soluble, dialyzable through a cellophane membrane (and therefore having a molecular weight of less than 25,000), resistant to postmortem autolysis and long-term freezing, and with no evidence of insulin, glucagon or histamine activity.

Poth [*28*] also gave injections of a saline extract of a tumor to dogs, but without significant effect on acid production. Gregory and his associates [*14*] obtained 1.4 gm. of an ulcerogenic adenoma. The solitary tumor had been removed from the head of the pancreas by Stammers. This brought prompt relief of ulcer symptoms, although no other ulcer surgery was performed. Intravenous injections of saline extracts from 600 mg. of this tumor were given to a dog with a Heidenhain pouch and to the standard rat preparation of Ghosh and Schild [*13*]. Contrary to the findings of Osborne's group, no evidence of any gastric stimulant was obtained from this simple saline extract. Chemical analysis showed only trace amounts of histamine.

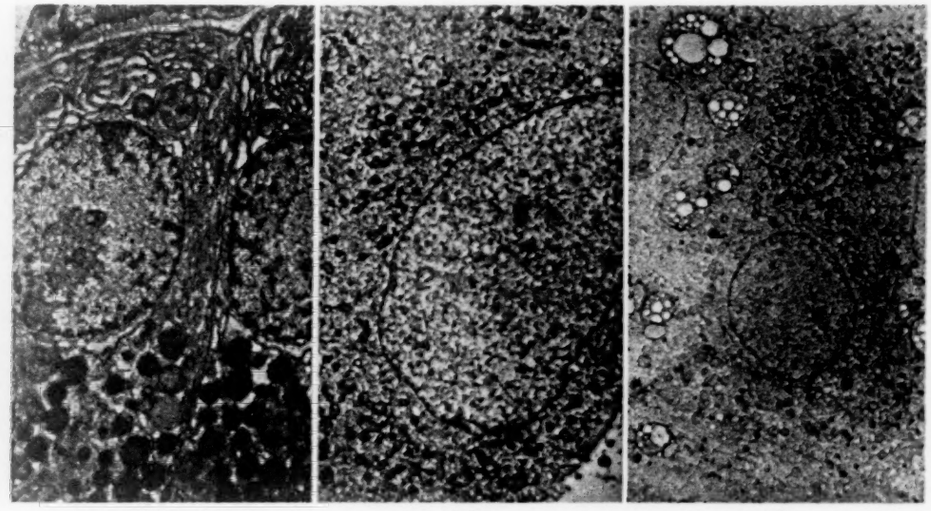
A second sample of the same tumor was prepared by a method used for the extraction of gastrin from hog antral mucosa [*15*]. Two separate samples were prepared and given as subcutaneous injections to dogs with Heidenhain prepared pouches. One also had a gastric fistula. These extracts produced prompt outpouring of gastric acid from both the Heidenhain pouch and the intact innervated stomach. Little or no pepsin was secreted. Such a response, acid without pepsin, is typical of the antral hormone, gastrin. Quantitatively, the tumor in these two samples was calculated to be, respectively, forty-five and thirty-three times as potent, gram for gram, as hog antral mucosa.

Gregory [*14*] and his group believe the tumor contains a substance chemically and physiologically similar to gastrin. Its activity is not thought to be due to insulin or histamine, nor does it cause the release of histamine upon intravenous injections.

More than eighty cases of ulcerogenic tumor of the pancreas have been reported and over 50 per cent of these have been malignant [*51*]. Table II. Metastases have occurred to the peri-

TABLE II
ULCEROGENIC TUMOR OF PANCREAS

Non-Beta Islet Cell	Per cent
Carcinoma	50
Aberrant	20
Adenomatosis	10
Polyglandular	20



1A 1B 1C

FIG. 1. A, normal acinar. B, ulcerogenic tumor. C, normal islet. By comparison the ulcerogenic tumor is definitely not acinar in origin but resembles closely the normal non-beta islet cell. Electron microscopy × 9,600.

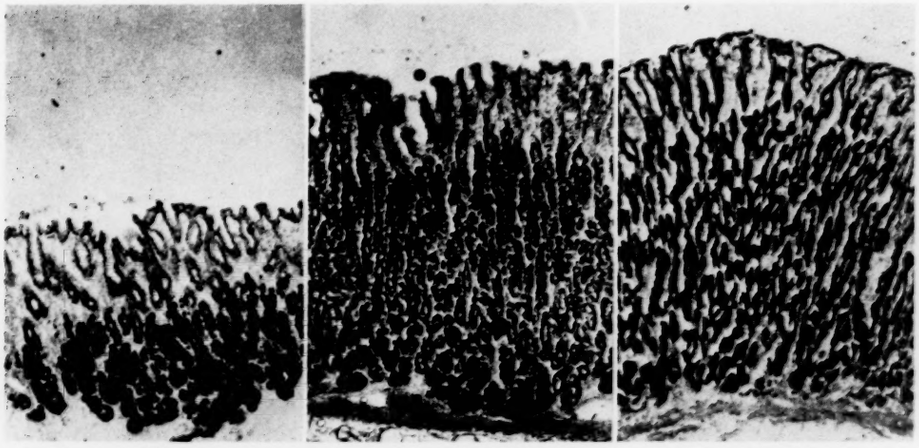
pancreatic lymph nodes and liver, and in one instance to the lung. The metastases have definitely been shown to produce the ulcerogenic factor, regardless of size. Grossly, these tumors have been nodular and from yellow-gray to reddish brown in color, depending upon their vascularity. In addition, about 20 per cent of the ulcerogenic tumors have been in an aberrant location, usually as whitish plaques varying up to 1 cm. in diameter in the juxta pancreatic wall of the duodenum, as described by Wermer [*45*] and Oberhelman [*24*]. Ten per cent of these patients have had diffuse adenomatous transformation of the islets throughout the pancreas. This change is almost always seen in association with adenomatosis of other endocrine glands. Additional endocrine tumors have been observed in about 20 per cent of the collected cases of ulcerogenic tumor.

One of the principal drawbacks in the study of this disease has been the inability to identify the responsible islet cell type. Present staining technics do not give reproducible results. The alpha cell, suspected first, comprises the principal cell type in only a few of the tumors. Glucagon, a secretion of the alpha cell, is not ulcerogenic, as Poth [*29*], Janowitz [*9*] and others had shown. The delta cell is the most difficult to identify; it has come under the closest scrutiny but without conclusive results. Microscopic diagnosis of these tumors is difficult, and frequently no distinction has been made between islet and acinar adenocarcinoma. Histochemical and electron microscopic studies suggest that the tumor is of islet cell origin but do not identify the specific islet cell type [*7*]. Anatomically, the tumor cells are aligned along the capillaries in a manner characteristic of endocrine tissue; this points to the secretory capacity of these cells.

Electron microscopic pictures provide more convincing proof of the islet cell origin of the ulcerogenic tumor cells. There is a marked similarity in the size and distribution of the intracellular chromatin material and mitochondria in the islet and tumor cells as opposed to the acinar cells. (Fig. 1.)

Histochemical staining of the gastric mucosa in patients with ulcerogenic tumors shows a hyperplastic transformation of the gastric glands which may extend down to and include the pylorus, as noted by Porter [*27*] and Rudolf et al. [*33*]. There is an accompanying marked increase in the number of parietal cells. These changes are known to occur in experimental animals under prolonged stimulation by histamine [*34*]. (Fig. 2.)

Powerful ulcerogenic stimulation, from the non-beta islet tumors, of an increased parietal cell mass in the stomach probably accounts for the gigantic gastric secretion seen in some of these patients. As pointed out in earlier publications, the tumor should be suspected when the twelve-hour night secretion approaches 2,000 cc. Considerably greater volumes (as much as 14 L.)



2A 2B 2C

FIG. 2. A, normal. B, ulcer. C, ulcerogenic. The increased parietal cell mass explains the gigantic volumes of acid gastric juice commonly observed in association with ulcerogenic tumor of the pancreas. Histochemical staining, parietal cells with lactic dehydrogenase.

have frequently been recorded. Gastric secretion seems to be cyclic in some patients, with wide variations both in acid content and total volume [*3*].

Other than the high gastric acid output, there is no test at present which is more than suggestive of the presence of a non-beta islet cell tumor. Barium contrast studies of the stomach, duodenum and small bowel may be contributory. Primary jejunal ulcers are, of course, highly suggestive, as well as deformities of the third part of the duodenum, some of which have been interpreted to be regional enteritis.

Wermer [*45*] has pointed out the frequency of deformity in the mucosal pattern of the second part of the duodenum because of the intraluminal projection of aberrant islet tumors.

Weber et al. [*43*] have described a distinctive, "lace-like or cobweb" pattern on roentgenograms of the small bowel in a small number of patients; this, they believe, is due to marked motor irritability and thickening of the valvulae conniventes. Whether or not this finding will have diagnostic value remains to be seen.

The clinical characteristics and laboratory abnormalities associated with the non-beta islet cell tumor all seem to relate to the gigantic output of acid by the stomach. For the most part, these patients have responded poorly or not at all to intensive medical treatment. Radiation to the stomach also has been without effect. This may be on the basis of the increased parietal cell mass extending down to the pylorus, and to the edematous, thickened wall of the stomach.

The pancreas should be visualized and carefully palpated by the surgeon in every patient operated upon for peptic ulcer. This is especially important in the presence of large volumes of gastric juice and in patients with early recurrence following a previous surgical procedure. The finding of a primary jejunal ulcer or perforation in a patient without a history of previous gastric surgery makes a careful search for non-beta islet cell tumors of the pancreas mandatory! The duodenum should be mobilized in order that any irregularities due to aberrant pancreatic tumors within its wall can be palpated. The greater omentum should be separated from the colon and the pancreas thoroughly inspected. Since these tumors are commonly quite small and located anywhere within the gland, they are easily overlooked. Obvious tumors should be removed along with some adjacent pancreatic tissue. A study of the latter may provide evidence of adenomatosis. If nothing is found, a biopsy specimen of the inferior margin of the body or tail of the pancreas may be taken to determine the presence or absence of adenomatosis of the islets. Since approximately half of these tumors are malignant, the adjacent lymph nodes as well as the liver should be carefully inspected for evidence of metastasis. Occasionally the diagnosis has been made from the biopsy of a peripancreatic lymph node. The left half of the pancreas can be safely removed for detailed examination with little risk to the patient.

The treatment of this disease is primarily surgical. Although the surgeon may identify

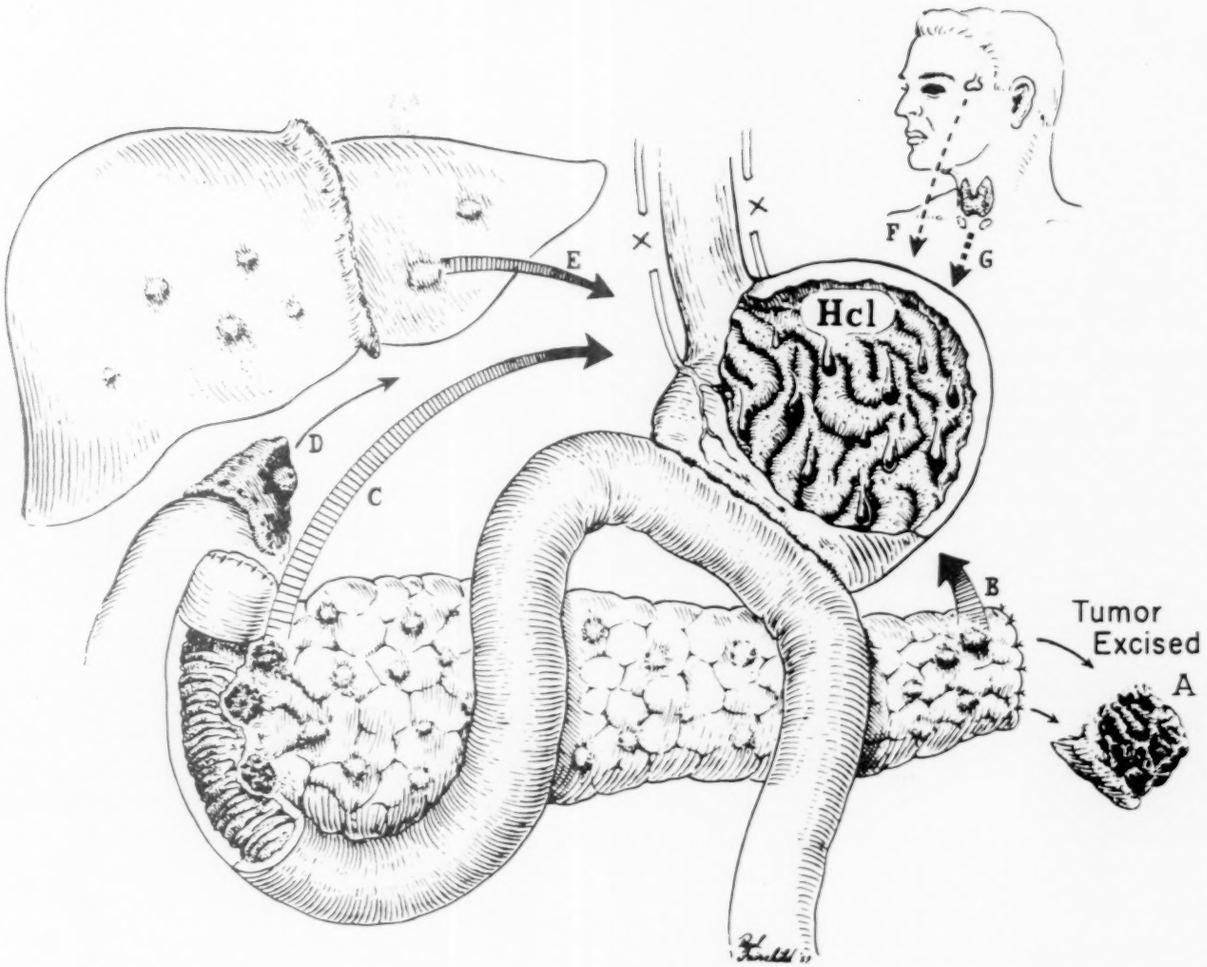


FIG. 3. Schematic illustration showing possible multicentric sources for powerful stimulation of the remaining gastric glands after excision of obvious tumor. The manifold origin of stimulation emphasizes the wisdom of total gastrectomy rather than total pancreatectomy.

and remove the primary tumor in the pancreas, this does not insure control of the peptic ulcer diathesis (although this has occurred in three instances) [*14,21,48*]. Potent ulcerogenic stimulation can occur from the various endocrine tumors already mentioned, as well as from aberrant and metastatic non-beta islet cell tumors. For this reason, the surgeon must direct his attention to removal of the target organ, the stomach. Total gastrectomy is advised when there is proof of the pressure of a non-beta islet cell tumor. Although solitary tumors have been removed in several patients, there are many more instances in which total gastrectomy has subsequently been required after failure of a lesser procedure. Since half of these tumors are malignant, 20 per cent are aberrant, 10 per cent are diffusely distributed throughout the pancreas and 20 per cent occur in association with additional endocrine tumors, the dangers of persistent and potent stimulation of retained gastric mucosa are obvious. Total pancreatectomy would succeed in eliminating only one of the many sources of stimulation. Furthermore, since half of the tumors are malignant, the danger of difficulty from metastasis is a real one.

If ulceration recurs after pancreatectomy, total gastrectomy would become mandatory, and the patient would then present a very complex problem in daily replacement therapy. Patients who have undergone total gastrectomy alone, on the other hand, have managed to maintain their ideal weight and have required only monthly injections of vitamin B_{12} to prevent pernicious anemia. Regardless of the age of the patient and the presence of obvious metastasis to

the liver, total gastrectomy should be performed to avoid the discomfort of early recurrence.

The coexistence of ulcer and beta-cell insulinomas of the pancreas is rare; there are only two reported cases. The insulinomas and the ulcers should be dealt with independently [*30*].

Polyglandular Adenomas. The polyglandular syndrome has been known for years, but Wermer [*44*] first called attention to the frequency of associated peptic ulceration of the upper gastrointestinal tract. This incidence has proved to be approximately 40 per cent.

In 1953 Underdahl and associates [*41*] described the endocrine polyglandular syndrome as comprising the simultaneous occurrence of tumors of two or all three of the following endocrine glands: pituitary, parathyroid and pancreatic islets. The polyglandular syndrome is characterized by the presence of multiple tumors within the gland, suggesting diffuse adenomatosis. Microscopically these adenomas are usually comprised of all the cell types of the particular gland involved, in contrast to the "pure cell" type of the usual adenomas. Microscopically these tumors in the pancreas tend to have a peculiar ribbon-like appearance due to the arrangement of the tumor cells along the wall of the blood vessel.

Wermer [*45*] has expanded this syndrome to include adenomas of the adrenal cortex and thyroid gland, as well as certain non-endocrine anomalies, such as giant gastric rugae, Menetrier's disease and lipomas in various locations. These minor components of the syndrome are not necessary in establishing the diagnosis. Wermer [*44*] is of the opinion that peptic ulceration in these patients with the polyglandular syndrome is hereditary and should not be attributed to secretion of any of the involved endocrine tumors.

Of the approximate thirty-eight patients with polyglandular syndrome collected from the literature, seventeen have had associated peptic ulceration. Thirteen patients were subsequently studied at either operation or autopsy and all had non-insulin producing islet cell tumors of the pancreas. In other words, there were no patients with polyglandular disease and peptic ulcer completely studied who did not have a non-beta islet cell tumor. The frequency of this association seems to emphasize the role of the non-insulin producing pancreatic islet cell tumor as the probable source of stimulation in the production of ulcer.

SUMMARY

There is increasing evidence that certain non-beta islet tumors of the pancreas play a major role in the etiology of intractable ulcer. The type of cell as well as the secretion responsible has thus far defied identification, despite intensive investigation. Extraction procedures on tumors removed at operation have yielded a substance similar to but thirty-five times as potent as gastrin.

Hyperfunctioning parathyroid tumors have been associated with peptic ulcer in about 13 per cent of patients. The incidence of ulcer in association with tumors of the beta islet cells, pituitary and adrenals is low enough to be a chance association.

The peptic ulcers associated with endocrine adenomas, especially of the pancreas, notoriously resist the usual medical therapy and account for a small percentage of the failures following intensive medical and radical surgical attempts at control of the acid factor. Removal of the offending adenoma will cure the ulcer in patients with hyperparathyroidism. However, nothing short of total gastrectomy will suffice in patients with non-beta islet cell tumors, due to the ubiquity of their metastases and aberrancies, all of which are capable of exerting a powerful influence on acid secretion of the stomach.

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Peptic Ulcer in Primary Hyperparathyroidism*

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Numerous reports of peptic ulcer disease associated with hyperparathyroidism have appeared in the literature since Gutman et al. [*1*] first noted the frequency of gastrointestinal symptoms in patients with parathyroid adenomas, followed by Rogers' [*2,3*] suggestion that peptic ulcer disease was aggravated by this disorder. The frequency with which the two diseases coexist is difficult to evaluate, since many of the reports cite isolated instances published specifically because of the striking relief of abdominal distress following removal of the parathyroid tumor, or because of aggravation of the hypercalcemia by an ulcer regimen. A more definitive concept of the relationship between the two diseases may be attained by studying the behavior and incidence of peptic ulcer in large unselected series of patients with hyperparathyroidism.

The present paper proposes to describe peptic ulcer disease as it occurred in our own group of patients with primary hyperparathyroidism, and in a composite review of several large series of published cases. Experimental data, relating parathyroid hormone, calcium metabolism and gastric function, will be presented.

Peter Bent Brigham Hospital Series

Selection of Patients. Between the years 1932–1959 the diagnoses of hyperparathyroidism, parathyroid adenoma or osteitis fibrosa cystica were recorded for 110 patients. Eliminating all patients with secondary hyperparathyroidism, hypercalcemia of other etiology, and asymptomatic parathyroid adenoma discovered, incidentally, at autopsy, thirty-nine subjects remained with primary hyperparathyroidism. (Table I.) Of these, twenty-eight were histologically proved, including five subjects with primary hyperplasia, twenty-two with a solitary parathyroid adenoma, and one with a parathyroid carcinoma. The remaining eleven patients were categorized as "probable" hyperparathyroidism on the basis of the typical clinical picture associated with serum calcium levels above 6.0 mEq./L. Hypercalciuria was present in five patients, and serum phosphorus levels were below 1.0 mM/L. in seven patients.

Peptic Ulcer Disease. The incidence of this disease is shown in Table II. Roentgenographic examinations were performed in thirteen patients and postmortem examinations in three of the twenty-eight patients with proved primary hyperparathyroidism. The diagnosis of ulcer was unequivocally established in only one instance, a forty-one year old woman who suffered an acute gastric ulcer with perforation two years prior to the appearance of bone pain and renal calculi. Two additional patients stated that peptic ulcer had been diagnosed previously, but gastrointestinal roentgenograms taken at this hospital revealed no abnormalities despite persistent symptoms of ulcer. In three other subjects with typical symptoms of ulcer, roentgenograms repeatedly failed to demon-

Table I

Patients with Primary Hyperparathyroidism

Proved (28)		Probable (11)	
Solitary adenoma	22	Serum calcium over 6.0 mEq./L.	11
Primary hyperplasia	5	Serum phosphorus below 1.0 mM/L.	7
Carcinoma	1	Urine calcium over 200 mg./day	5

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TABLE II*

PEPTIC ULCER AND GASTROINTESTINAL SYMPTOMS IN PRIMARY HYPERPARATHYROIDISM

Symptoms	Hyperparathyroidism	
	Proved (28)	Probable (11)
Peptic ulcer (proved by roentgenograms or pathologic reports)	1 (gastric)	2 (duodenal)
Typical symptoms of peptic ulcer (no ulcer demonstrated)	6	2
Normal gastrointestinal roentgenogram	2	1
"Gastroduodenitis" by roentgenogram	1	0
Previous "ulcer" by history; normal results of gastrointestinal series at present	2	0
No gastrointestinal roentgenogram taken	1	1
Atypical upper gastrointestinal symptoms (heartburn, nausea, vomiting)	8	1
Normal gastrointestinal roentgenogram	1	0
No gastrointestinal roentgenogram taken	7	1
No upper gastrointestinal symptoms	13	6
Normal gastrointestinal roentgenogram	5	1
Gastritis on roentgenogram	1	0
No gastrointestinal roentgenogram taken	7	5

* Of the thirty-nine patients with primary hyperparathyroidism the gastrointestinal tract was examined in seventeen (proved peptic ulcer, three; typical symptoms of ulcer, no ulcer found six). The gastrointestinal tract was not examined in twenty-two patients (typical symptoms two).

strate an ulcer. Atypical upper abdominal symptoms (pyrosis, postprandial nausea and vomiting) were noted in eight other subjects; in one of these subjects a gastrointestinal series had been performed and reported as having normal results.

Among the eleven patients with "probable" hyperparathyroidism, gastroduodenal roentgenograms were performed in only four patients. In two of these patients a duodenal ulcer crater was seen. Two other subjects presented typical ulcer symptoms. The gastrointestinal roentgenograms performed in one revealed no abnormalities.

TABLE III

GASTRIC ANALYSES IN PROVEN HYPERPARATHYROIDISM

Case No.	Gastric Acidity (mEq./L.)	Clinical Gastrointestinal Symptoms
1	"Low" fasting acidity	Ulcer symptoms, negative results of gastrointestinal roentgenograms
2	Fasting, no free acid Histamine, free acid present	Ulcer symptoms, negative results of gastrointestinal roentgenograms
3	Fasting, 0 free/44 total	Ulcer symptoms, gastrojejunitis
4	Basal, 0 free/6 total Histamine, 59 free/99 total	Heartburn, no gastrointestinal roentgenograms
5	Basal, 0 free	Biliary cirrhosis and gallstones
6	Histamine, 0 free/12 total	Gallstones with nausea and emesis
7	Preoperatively Fasting, 0 free/2 total Histamine, 24 free/33 total Postoperatively (adenoma excised) Fasting, 0 free/6 total Histamine; 20 free/25 total	Cramps in the right upper quadrant of the abdomen, nausea and vomiting with normal results of gastrointestinal roentgenograms, nonfunctioning gallbladder by oral cholecystography

Thus peptic ulcer was unequivocally demonstrated in only three of the thirty-nine patients (7.7 per cent). However, examination of the upper alimentary tract by roentgenograms, surgery or autopsy was performed in only seventeen instances.

Gastric Analyses. Data concerning gastric analyses are shown in Table III. Gastric acidity appeared to be low or normal in the seven instances in which gastric analyses were performed although three of these patients presented symptoms of peptic ulcer. In the only subject studied pre- and postoperatively, there was no change in basal or histamine-stimulated acid concentration after parathyroidectomy.

Clinical Features. Other clinical data are shown in Tables IV and V. In both the proved and "probable" patients with hyperparathyroidism, the mean age at the time of diagnosis was forty-seven years. The disease was approximately twice as common among women (twenty-four of thirty-nine subjects). Genitourinary calculi were the most prevalent manifestations of the disease, followed by skeletal involvement. Gallstones were present in nine of the thirty-nine patients, and produced symptoms in five. Two other subjects exhibited a non-filling gallbladder

TABLE IV

CLINICAL ASPECTS OF HYPERPARATHYROIDISM

Data	Proved Cases (28)	Probable Cases (11)	Entire Series
Sex			
Men	11	4	15
Women	17	7	24
Mean age (yr.)	47	47	47
Urological			
Renal stones	21	7	28
Nephrocalcinosis	1	0	1
Pyelonephritis, no stones	1	0	1
Skeletal			
Bone cysts	7	2	9
Pathologic fractures	2	0	2
Demineralization or changes in phalangeal tufts	7	1	8
No abnormalities	14	8	22
Band keratopathy	0	2	2
Thyroid			
Toxic nodular goiter	0	1	1
Papillary carcinoma	1	1	2
Non-toxic colloid goiter	3	1	0

TABLE V
HEPATOBILIARY DISEASE IN HYPERPARATHYROIDISM

Data	Proved Cases (28)	Probable Cases (11)
Cholelithiasis		
Roentgenogram	4 (all symptomatic)	3 (all symptomatic)
Autopsy	2 (one symptomatic)	0
Non-filling gallbladder with upper abdominal symptoms	2 (one had no stones at operation)	0
Complications		
Cholecystitis and pancreatitis, acute and fatal	1	0
Biliary cirrhosis	1	0
Pancreatitis, acute and chronic, without cholelithiasis	1	0

TABLE VI
PEPTIC ULCER IN PROVED, PRIMARY HYPERPARATHYROIDISM
(COMPOSITE SERIES)

Data	Howard [5,10]	St. Goar [6,11]*	St. Goar [7]	Moses [8]†	Hellström [9]	Present Series	Total
Hyperparathyroidism	63	136	45	36	121	28	429
Peptic ulcer	8	9	4	3	14	1	39
Duodenal	7	7	2	2	13	0	31
Gastric	1	2	2	1	1	1	8
Hyperparathyroidism (men)	29	39	16	11	35	11	141
Peptic ulcer	4	2	3	2	10	0	21
Duodenal	3	0	1	1	9	0	14
Gastric	1	2	2	1	1	0	7
Hyperparathyroidism (women)	34	97	29	25	86	17	288
Peptic ulcer	4	7	1	1	4	1	18
Duodenal	4	7	1	1	4	0	17
Gastric	0	0	0	0	0	1	1

* St. Goar's (1954) series [6] from the Massachusetts General Hospital reported 137 patients, twelve of whom had peptic ulcers. However, we have discarded one patient with ulcer with secondary hyperparathyroidism, and two patients whose ulcers were considered unproved radiologically, leaving 136 patients with primary hyperparathyroidism and nine proved ulcers.

† In Moses' 1958 series [8] patient number four died without surgical or postmortem examination of the parathyroids, and is therefore excluded from our series of pathologically proved hyperparathyroidism.

at cholecystography. Complications included acute, fatal cholecystitis and pancreatitis in one instance and severe biliary cirrhosis in another. An additional subject, previously reported on by Hoar and Gorlin [4], had acute and chronic pancreatitis associated with a normal gallbladder.

COMPOSITE REVIEW OF SERIES FROM THE LITERATURE

Selection of Cases. Including our own twenty-eight patients, there are six large, unselected series [5–9]. These series are comprised of 429 patients with histologically proved primary hyperparathyroidism in whom the incidence of peptic ulcer was noted, and in whom the criteria for the diagnosis of ulcer could be assessed, either from the reports themselves or from unpublished data graciously furnished by the authors [10,11].

Incidence of Ulcer. The incidence of ulcer is shown on Table VI. There were thirty-nine subjects with a proved peptic ulcer established

TABLE VII*

MEAN AGES AT TIME OF PARATHYROID EXPLORATION

(COMPOSITE SERIES)

Data	Howard [10]	St. Goar [11]	St. Goar [7]	Moses [8,12]	Hellström [9]	Present Series	Total
Patients with ulcer	53	40	55	49	49	41	48
Patients without ulcers	44	45	45	47	47	49	46

* Based on thirty-eight patients with ulcer and 376 patients without ulcer. Information not available from Howard (1953) three patients, St. Goar (1954) two patients, and Moses (1958) ten patients.

TABLE VIII

TIME RELATIONSHIP OF ULCER SYMPTOMS AND PARATHYROID SYMPTOMS*

(COMPOSITE SERIES)

Data	St. Goar [6,11]	St. Goar [7]	Moses [8]	Hellström [9]	Present Series	Total
Ulcer symptoms with or after parathyroid symptoms	3	1	1	4	0	9
Ulcer symptoms preceded parathyroid symptoms by two years or more	6	3	2	10	1	22
Ulcer symptoms preoperatively	4	3	3	7	0	17
Disappear postoperatively	2	1	2	3	0	8
Persist or recur postoperatively	0	1	0	4†	0	5
Not stated	2	1	1	0	0	4
No ulcer symptoms preoperatively‡	3	0	0	7	1	11
Recur postoperatively	2	0	0	0	0	2

* Information not given for Howard's cases in 1953 [5], which are therefore omitted from this tabulation.

† In one case a patient had multiple benign insulinomas and a prior subtotal gastrectomy. His symptoms of ulcer persisted despite the gastrectomy and parathyroidectomy.

‡ Two of St. Goar's patients in 1954 [6] and one in 1957 [7] were permanently relieved of symptoms from ulcer by subtotal gastrectomy performed prior to parathyroidectomy. These are, therefore, omitted from the tabulation.

by surgery, autopsy, or the finding of a gastroduodenal crater or deformity on roentgenographic examination, an over-all incidence of 9.1 per cent. Typical symptoms of peptic ulcer were noted in twenty-eight additional subjects in whom no gastroduodenal abnormalities were demonstrable at fluoroscopy or postmortem examination.

Age. The mean age of the patients with peptic ulcer was forty-eight years, and of the patients without ulcer forty-six years at the time the diagnosis of hyperparathyroidism was established. (Table VII.)

Sex. There were 141 men and 288 women among the 429 patients. Peptic ulcer was found in twenty-one men and eighteen women, an ulcer incidence of 14.9 per cent and 6.2 per cent, respectively. (Table VI.)

Location of Ulcer. The ulcer was found in the duodenum in thirty-one instances and in the stomach in the remaining eight (two of these patients also had a duodenal scar). Duodenal ulcer predominated in men (fourteen of twenty-one) and was present in all but one of the eighteen women. In the one exception a deformed duodenal cap was later found in addition to the gastric ulcer. (Table VI).

Complications of Ulcer. Complications of peptic ulcer were present in 33 per cent. Six patients suffered major hemorrhage, six had a perforated ulcer and one had pyloric obstruction. Five patients underwent subtotal or total gastrectomy because of intractable ulcer distress.

Time Relationship. Among the thirty-one patients in whom data were available in this respect, twenty-two had typical symptoms of

TABLE IX
PARATHYROID PATHOLOGY
(COMPOSITE SERIES)

Sources of Cases	Single Parathyroid Adenoma	Multiple Parathyroid Adenomas	Polyendocrine Adenomas	Present Series	Parathyroid Carcinoma
Entire Series					
Howard [5,10]	57	5	1	0	0
Hellström [13]*	39	0	0	7	0
St. Goar [6]	114	9	0	11	2
St. Goar [7]	41	2	0	0	1
Moses [8,12]†	22	2	1	1	0
Present series	22	0	0	5	1
Total (343 cases)‡	295	18	2	24	4
Per cent	86.0	5.2	0.6	7.0	1.2
Ulcer patients only					
Howard [5,10]	6	1	1§	0	0
St. Goar [6]	8	1	0	0	0
St. Goar [7]	2	1	0	0	1
Moses [8,12]	2	1	0	0	0
Hellström [9]	12	0	1‖	1	0
Present series	1	0	0	0	0
Total (39 cases)	31	4	2	1	1
Per cent	79.5	10.3	5.1	2.6	2.6

* Hellström's 1959 series [9] did not state the pathologic findings for the entire group, but only for the patients with ulcer. Therefore, the forty-six patients in his 1954 report [13] are taken as a representative sample of the later, larger series.

† Data available for only twenty-six of Moses' patients [12]. Note that one of his subjects had polyendocrine adenomas (two parathyroid, chromophobe pituitary, pancreatic islet cell) without peptic ulceration.

‡ Black in 1956 [14] reported on 207 patients with primary hyperparathyroidism, of whom 17 per cent had peptic ulcer. He did not give the criteria for diagnosis of ulcer, or the pathologic parathyroid findings in the ulcer group. However, his pathologic data for the entire series are almost identical with our following composite series: single adenoma, 177 (86 per cent); multiple adenoma, eight (4 per cent); polyendocrine adenomas, five (2 per cent); primary hyperplasia, fifteen (7 per cent); and carcinoma, two (1 per cent).

§ Multiple parathyroid adenomas with non-beta cell tumor of the pancreatic islets, a true Zollinger-Ellison syndrome.

‖ Single, parathyroid adenoma with multiple pancreatic insulinomas (benign), and an intractable bizarre ulcer diathesis.

peptic ulcer at least two years prior to the onset of clinical hyperparathyroidism. (Table VIII.)

Effect of Parathyroidectomy. The relationship of parathyroidectomy to gastrointestinal symptoms could be ascertained in twenty-eight of the thirty-nine patients. (Table VIII.) Typical symptoms of ulcer immediately prior to surgery, usually with a radiologically demonstrable ulcer crater, were noted in seventeen instances. After parathyroidectomy was performed eight of seventeen patients experienced lasting relief. However, five others continued to suffer ulcer distress postoperatively, or experienced a subsequent relapse, occasionally with hemorrhage, after temporary initial improvement. Of eleven patients who were asymptomatic immediately before parathyroidectomy two had recurrent severe ulcer distress with hemorrhage, one and eight years postoperatively.

Pathologic Condition of the Parathyroid Glands. Among the ulcer patients, thirty-one had a single parathyroid adenoma and four showed multiple parathyroid adenomas. There were two instances of multiple endocrine adenomas, one of primary parathyroid hyperplasia, and one of parathyroid carcinoma. In the over-all series the incidences were similar, except for a barely significant ($P < 0.05$) excess of multiple parathyroid adenomas among the ulcer patients. (Table IX.)

TABLE X
GASTRIC ANALYSES IN PROVED HYPERPARATHYROIDISM
(ISOLATED CASES FROM THE LITERATURE)

Author	Gastric Acidity (mEq./L.)	Clinical Gastrointestinal Symptoms
Herzenberg [26]	Fasting, 0 free/8 total	Previous gastric ulcer; died in acute parathyrotoxicosis with hemorrhagic gastritis at autopsy
Morelle [27]	Fasting free acidity Preoperative, absent Postoperative, present and normal	Ulcer symptoms, roentgenograms gave negative results
Mellgren [28]	Fasting, 0 free/25 total Test meal, 45 free/65 total	Ulcer symptoms, roentgenograms gave negative results
	Test meal, 0 free/45 total	Now marked gastrointestinal symptoms with acute parathyrotoxicosis; at autopsy, healed duodenal ulcer and marked gastric calcinosis
Rogers [2]	Fasting, 69 free/82 total	Duodenal ulcer
Rogers [2]	Fasting, 56 free/68 total	Duodenal ulcer
Schneider, Robnett [29]	Test meal, 32 free/48 total	Duodenal ulcer
Elkeles [30]	Fasting, no free acid, histamine, free acid present	Active duodenal and gastric ulcers
Howard et al. [5]	Preoperatively Fasting—9 free Postoperatively Alcohol—42 free	Duodenal ulcer, recurring ten months after removal of a parathyroid adenoma
Underdahl, Woolner and Black [31]	Fasting, 114 free/130 total	Duodenal ulcer; polyendocrine adenomas with pituitary tumor
Underdahl, Woolner and Black [31]	Fasting, 74 free/104 total	Duodenal ulcer two years after three adenomatous parathyroids excised; polyendocrine adenomas with hyperinsulinism
Hellström [9]	Preoperatively Fasting, 0 free/0 total Histamine, 74 free/84 total Postoperatively Fasting, 0 free/15 total Histamine, 15 free/30 total	Previous subtotal gastrectomy for duodenal ulcer; now active stomal ulcer (gastrojejunal); multiple pancreatic insulinomas later removed when total gastrectomy performed.

REVIEW OF EXPERIMENTAL DATA

The chronic duodenal or gastric ulcer seen in clinical hyperparathyroidism in man has not been reproduced in experimental animals by the administration of parathyroid hormone, intravenous calcium salts or vitamin D. Large doses of parathyroid extract do, however, produce intramucosal hyperemia, petechiae, hemorrhages, and necrosis of the fundic glands within the stomachs of dogs and rats [15–22], lesions which are distinctly different from those observed in man. Multiple, acute, superficial ulcerations of the stomach may develop in rats after two to ten days of the massive administration of parathyroid hormone [21,22]. However, severe hypercalcemia *per se* induced by the administration of vitamin D or intravenous calcium salts may produce identical lesions [15,22]. Although Hellström [9] has stressed the occurrence of peptic ulcer in patients with mild, chronic hyperparathyroidism, no gastric lesions have been produced in animals by prolonged administration of small doses of parathyroid hormone [23,24] or by larger doses of parathormone if marked hypercalcemia is avoided [25].

The administration of parathyroid hormone does not appear to influence gastric secretion consistently in man. In seven of our own patients

(Table III) and in eleven isolated cases from the literature [*2,5,9,26–31*] (Table X) the concentrations of gastric acid were within or below the normal range in all but four cases, although nine had proven peptic ulcer disease. Two of the four patients with increased gastric secretion had multiple endocrine adenomas, characteristically associated with gastric hyperacidity. In three of four patients in whom gastric secretion was studied pre- and postoperatively, removal of the parathyroid adenoma did not decrease gastric acidity. The one exception was a patient with multiple endocrine tumors. Donegan and Spiro [*32*] found no significant change in the output of gastric acid after administration of parathyroid hormone or calcium gluconate to eight normal human subjects, or after excision of the parathyroid adenoma in five patients with hyperparathyroidism. Bauer et al. [*33*] reported a diminution in gastric acidity in human subjects given radiated ergosterol.

Experimental studies from this laboratory indicate that the administration of parathyroid hormone does not increase the gastric secretion of water, chloride, acid or pepsin in rats [*22*]. Babkin [*24,34*] and Schiffrin [*35*] have reported that the administration of the hormone decreased the postprandial gastric secretion of water and acid in Pavlov pouch dogs, but did not alter the histamine-induced secretion [*36*] or the secretion of denervated Heidenhain pouches. Similar secretory patterns were obtained following hypercalcemia induced by the administration of vitamin D or intravenous calcium salts [*24,34,35,37*]. These authors [*24,34,35*] concluded that parathyroid hormone primarily influences gastric secretion by hypercalcemic inhibition of vagal activity.

Although hypercalcemia may inhibit vagal activity, there may be a critical level of serum calcium below which the gastric glands cannot function normally, as suggested by Donegan and Spiro [*32*]. This may explain the reduced gastric secretion associated with hypoparathyroidism and hypocalcemia. In hypoparathyroidism in man [*32*] and tetany in infants [*38*] there is a markedly reduced gastric secretion which returns to normal as the hypocalcemia is corrected. Hyposecretion in rachitic rats is restored to normal following therapy with vitamin D [*39*]. Similarly, a decreased gastric secretion has been noted in thyroparathyroidectomized rats [*22,40, 41*], although the exclusive role of the parathyroid in these experiments is questionable since Sun et al. [*40*] have demonstrated identical secretory alterations in rats rendered hypothyroid by the administration of thiouracil or radioactive iodine. However, Keeton [*42*] and Chang and Sloan [*43*] report decreased gastric secretion during tetany in thyroparathyroidectomized cats and dogs, with an increase in secretion when the tetany is corrected by the administration of calcium.

Since gastric secretion is not increased by the administration of parathyroid hormone or hypercalcemia, hyperparathyroidism may induce peptic ulcer disease by some other mechanism. Many of the gastrointestinal symptoms of hyperparathyroidism have been attributed to altered gastrointestinal motility [*1,44*], presumably on the basis of impaired neuromuscular activity secondary to hypercalcemia [*45,46*]. There is, however, no well documented evidence that gastrointestinal activity is abnormal in hyperparathyroidism, nor is there any demonstrated relationship between neuromuscular activity and the genesis of peptic ulcer in this disease.

Calcinosis of the gastric wall has been implicated but there is no evidence that it produces peptic ulcer in patients with chronic hyperparathyroidism. Calcinosis and superficial ulcers occur in the same portions of the stomach in animals with acute parathyrotoxicosis. However, peptic ulcer is uncommon in hypoparathyroidism [*47*] and in acute hyperparathyroidism in man [*44,48,49*]. Moreover, on histologic examination of the stomach in patients with chronic hyperparathyroidism excessive calcification is not revealed [*50*]. On the other hand, medial arterionecrosis and calcification, not uncommonly seen in acute and chronic hyperparathyroidism in animals, may play a role in producing superficial gastric ulcerations [*17,51*], although there are no pertinent clinical studies in human subjects.

Recent studies have indicated that there may be a direct action of parathyroid hormone upon bone mucoprotein-mucopolysaccharide complexes [*52–54*], with the release of calcium as a consequence [*55–57*]. Excess of the hormone could conceivably liquefy gastric mucus, thus destroying its presumed function of protecting the mucosa against acid-peptic digestion [*58*]. Alternatively, it may directly destroy the ground substance of the gastric mucosa, a hypothesis which could account for the necrosis and calcification of the gastric glands occurring in

animals after the administration of excessive doses of parathyroid hormone [*17–20,59,60*]. These attractive hypotheses await experimental clarification.

COMMENTS

In our composite review of 429 unselected patients with proved primary hyperparathyroidism, the frequency of proved peptic ulcer was 9.1 per cent, which is considerably below the 24 per cent incidence first reported by Black in 1953 [*61*]. His series of 112 patients was omitted from the composite review because detailed data relative to the criteria for the diagnosis of ulcer were not available. Black [*62*], however, in a series of 161 patients with hyperparathyroidism operated upon between 1952 and 1957 has observed sixteen radiologically proved peptic ulcers, an incidence of 9.8 per cent, which closely approximates that of the composite review. With the inclusion of Black's sixteen patients with ulcer, and the four patients with equivocal ulcers from the Brigham series and St. Goar's group in 1954 (Table VI), the over-all incidence among 590 patients is only 10 per cent. Admittedly, this is a minimum figure, since in none of the reported series were more than half the patients subjected to gastrointestinal roentgenograms. However, in the vast majority of patients with gastrointestinal symptoms, and therefore those most likely to have a peptic ulcer, roentgenograms were taken. In any event, the true incidence of peptic ulcer in hyperparathyroidism approximates 10 per cent and certainly does not exceed 15 per cent. This is somewhat but not strikingly higher than the frequency of peptic ulcer among the population at large in similar age groups [*63–65*], which varies from 5 to 10 per cent depending upon the selection of cases and the diagnostic criteria employed.

In many respects the clinical features of peptic ulcer in hyperparathyroidism were not unusual. As in the general population [*66*], peptic ulcer was approximately two to three times as frequent in males, and duodenal ulcer outnumbered gastric ulcer 4:1. The 33 per cent incidence of complications due to ulcer is similar to that noted in peptic ulcer disease in general [*67*], although perforation appears to be unduly common in this small series of hyperparathyroid patients. Intractability of the ulcer was not a prevalent feature with the exception of two patients with polyendocrine adenomas.

There were, however, three distinctive features: (1) the striking preponderance of duodenal ulcer among the females (eighteen of nineteen cases), (2) the relatively high frequency of gastric ulcer among the males, (3) the absence of gastric hypersecretion.

Our composite figures indicate that there is generally no parallelism between the severity of distress due to an ulcer and the severity of the manifestations of hyperparathyroidism. Nearly half of the patients with ulcer had neither an active crater nor symptoms of peptic ulcer just prior to parathyroidectomy, when the symptoms of hyperparathyroidism were most prominent. Furthermore, in five instances the ulcer and its symptoms did not improve after parathyroidectomy, and in two patients the ulcer reappeared postoperatively after a long quiescent period prior to surgery. It should be emphasized that, in many cases, ulcer-like symptoms and vague abdominal complaints were observed in hyperparathyroidism in the absence of any demonstrable peptic ulcer. Consequently, the relationship of peptic ulcer disease to hyperparathyroidism appears to be exaggerated in the literature.

It is difficult to determine the true time of onset of either peptic ulcer or hyperparathyroidism, since it is well known that each of these diseases may exist for many years before the diagnosis is established [*68–70*]. However, two-thirds of the patients with ulcer noted the onset of ulcer symptoms at least two years, and often as long as twenty years prior to the clinical manifestations of hyperparathyroidism.

There was nothing distinctive about the clinical features of hyperparathyroidism in the patients in whom peptic ulcer developed. The diagnosis of hyperparathyroidism was established at approximately the same mean age in the ulcer and non-ulcer groups. Many of the reports utilized in our composite review have already stressed the similarity of the renal and osseous manifestations among the patients with ulcer and the remainder of the hyperparathyroid subjects.

Our tabulation of the pathologic condition of the parathyroid glands contradicts Hellström's [*9*] concept that primary parathyroid hyperplasia is more prevalent in hyperparathyroid patients with peptic ulcer disease, a conclusion drawn from a review of selected individual case reports. However, our data support his conclusion that multiple parathyroid adenomas, sometimes

occurring with polyendocrine tumors, are probably more common among the patients with ulcer.

Polyendocrine adenomas were present in one patient in whom there was no peptic ulcer, and in two of the forty patients with ulcer. Both of the patients in the latter group had multiple pancreatic tumors in addition to the parathyroid adenomas, and eventually total gastrectomy was required for cure of severe, intractable ulcer disease. In one patient, the pancreatic adenomas were of the true Zollinger-Ellison non-beta cell type [*10*], while the other had multiple insulinomas [*9*]. In neither case did removal of the parathyroid lesion affect the ulcer diathesis. Among eighty-one collected cases of the Zollinger-Ellison syndrome [*71*], only six patients had parathyroid adenomas with clinical hyperparathyroidism. Donaldson [*72*], in a review of the literature, found nine cases of polyendocrine adenomatosis with peptic ulcer in which pancreatic adenomas were absent. Four of these patients had parathyroid adenomas, but only two had clinical hyperparathyroidism. It is thus quite unlikely that parathyroid hyperfunction is the ulcerogenic factor in these syndromes, since clinical hyperparathyroidism was present in only eight of ninety patients.

Ellison, Abrams and Smith [*65*], in an analysis of 812 gastroduodenal ulcers in a series of 20,000 consecutive autopsies, noted that no adenomas and only five cases of parathyroid hyperplasia were present. Although it is not indicated whether the hyperplasia was of the primary or secondary type, none were associated with clinical hyperparathyroidism, further emphasizing the infrequency of parathyroid dysfunction in peptic ulcer disease.

It seems evident from the collected data that hyperparathyroidism is not associated with a markedly increased incidence of peptic ulcer or with an unduly resistant form of the ulcer diathesis. This does not, however, negate the importance of detecting the coexistence of the two diseases, since milk and alkali therapy constitute a hazard to the patient with unrecognized hyperparathyroidism [*3*]. Moreover, an active peptic ulcer may lie hidden behind the cloud of non-specific gastrointestinal complaints accompanying hyperparathyroidism. Indeed, parathyroid hyperfunction should be considered when the ulcer symptoms, and the general condition of the patient, progressively deteriorate on good ulcer management.

The data at hand do not warrant the conclusion that there is a direct cause and effect relationship between hyperparathyroidism and peptic ulcer disease, in spite of the somewhat increased incidence. It is possible that their concurrence may be related to genetic factors promulgating both diseases in the same person. This concept has been suggested by Underdahl et al. [*31*], Wermer [*73*] and Moldawer et al. [*74*] for the polyendocrine adenoma syndrome. Jackson's [*75*] recent report of a family with a high incidence of both hyperparathyroidism and peptic ulcer suggests that the same may be true of the more common, single adenoma variety of parathyroid hyperfunction. Should, however, future studies prove that the two diseases are associated on a more direct basis, the relationship may reside in the destructive effects of excess parathyroid hormone upon the mucoid substances of the gastric mucosa and its secretions. The normal or reduced gastric secretion found in hyperparathyroidism exclude hypersecretion from the pathogenesis of peptic ulcer in this disease.

SUMMARY

1. Peptic ulcer proved by roentgenograms, surgery or autopsy was demonstrated in 9.1 per cent of a composite series of 429 unselected patients with primary hyperparathyroidism. A similar incidence of 7.7 per cent was noted in a smaller series of thirty-nine patients studied at the Peter Bent Brigham Hospital. Proved peptic ulcer in hyperparathyroidism appears to be only slightly more prevalent than that found among the general population.

2. Although primary hyperparathyroidism was twice as common among females, peptic ulcer in hyperparathyroidism was observed more frequently in men (14.9 per cent) than in women (6.2 per cent). Duodenal ulcer predominated among the men and was present in all but one of the eighteen women with peptic ulcer disease. The ratio of duodenal to gastric ulcer for both sexes was 3.7:1.

3. There were no unusual characteristics of peptic ulcer disease in hyperparathyroidism except for the high incidence of duodenal ulcer among women.

4. Symptoms of peptic ulcer were often observed in patients with hyperparathyroidism in the absence of a demonstrable peptic ulcer.

5. A review of the experimental data revealed that gastric secretion apparently is not increased

in either man or animals with hyperparathyroidism.

6. Peptic ulcer may not be directly related to hyperparathyroidism since (1) the symptoms of ulcer and hyperparathyroidism did not seem to parallel each other in severity, (2) the peptic ulcer generally preceded the onset of clinical hyperparathyroidism, and (3) the ulcers often persisted or became worse after removal of the parathyroid adenoma.

7. Multiple parathyroid adenomas and polyendocrine adenomas were more common in the patients with hyperparathyroidism in whom peptic ulcer developed than in the group as a whole.

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Ulcerogenic Drugs and Technics*

Experimental and Clinical

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THIS paper is primarily concerned with the relationship between pharmacological agents and peptic ulcer in man. Due to the extensive literature a thorough review of all the experimental and clinical investigations which may point to this relationship will not be attempted. Pertinent references in Kirsner's 1957 report on drug-induced peptic ulcer [*1*] and Lambert's 1958 comprehensive review on experimental ulcer production [*2*], in addition to those in the more recent literature, have provided the source material for this discussion.

Investigations working with animals have shown that the stomach and duodenum are vulnerable to the local and systemic effects of many biological compounds and medications. Acute ulceration, resembling that developing after experimental stress [*3*] and stimulation or injury to the hypothalamus and other parts of the brain [*4,5*], can be produced by the administration of acetylcholine [*6,7*], pilocarpine [*8*], insulin [*9*], Pitressin® [*10*] and urocholine [*11*]. As summarized by Kirsner [*1*] these lesions apparently begin as local hemorrhages and progress, as a result of the digestive action of gastric juice, to multiple erosions and superficial ulcerations located especially in the fundus of the stomach. The initiation of the chain of events leading to ulceration has been attributed to areas of ischemia secondary to spasm or stasis in mucosal blood vessels. Healing occurs rapidly with removal of the noxious agent; chronic ulceration is rare. There is overwhelming evidence that, regardless of the exact mechanism, the ulceration itself results from the failure of the gastroduodenal mucosa to withstand the digestive action of hydrochloric acid and pepsin.

In evaluating the relationship between a drug reaction and ulceration in man, one must assess not only the pharmacological action of the drug but also the effect of the disease itself, the possibility of the ulcer being coincidental, and the significance of the person's susceptibility to peptic ulcer formation. Susceptibility may be dependent upon psychogenic and/or physical factors, such as the functioning parietal cell mass and the inherent resistance of the mucosa to the digestive action of gastric juice.

EXPERIMENTAL DESIGN

The experimental design to investigate the ulcerogenic effect of the administration of a drug in man can be either similar or dissimilar to that in animals. Comparable studies with the same or different technics can determine the effect of drug administration upon acid, pepsin, neutralizing and buffering secretions and/or upon the protective mucus barrier. One of the most practical tools in this evaluation in man is the measurement of the output of free total hydrochloric acid per unit of time, as well as the viscosity of gastric secretion before, during and after the administration of the drug. Although continued aspiration by use of the Gomco suction apparatus is fairly reliable, the most accurate results are obtained by continuous hand suction [*12*]. Blood and urinary pepsinogen studies can provide additional information.

Gastric mucosal changes are best observed by gastroscopy and repeated gastric biopsy specimens but indirect evidence that gastritis has resulted from prolonged administration of a drug might be elicited by repeated intubation and tubeless examinations. Poliner and Spiro [*13*] have reported observations which might allow a presumptive diagnosis of gastritis if a significant decrease in gastric acid and pepsin secretion associated with an elevated plasma or urinary pepsinogen should occur as a consequence of drug therapy. This is consistent with the report of Rider and co-workers [*14*] who found a decrease of gastric acidity associated with an increase in uropepsin activity as the first evidence of injury to the gastric mucosa by radiation. Repeated gastrointestinal series and changes in subjective symptoms can contribute further information to aid in assessing the relationship

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between drug therapy and ulcer formation. Finally, the incidence of new ulcers in patients receiving a specific drug must be compared with that occurring in a comparable population during the period of drug therapy.

Experiments in animals can be designed to provide more specific information relative to dose, route of administration, time relationship, appearance and course of any associated gastritis, hemorrhage, erosion and/or vascular changes relating to the ulcer formation.

In transposing the results of experiments in animals to man, it may be recognized that there may be differences in susceptibility to the ulcerogenic effect of the same drug. However, dissimilar findings among different animals and man may relate not only to their inherent tissue resistance and the local or systemic effect of the drug but also to variations in the metabolic degradation or biologic half-life of the drug. Examples of the latter are noted with histamine [*2*] and phenylbutazone [*15*]. The administration of a much higher dose of histamine per kilogram of body weight is required in the rat than in the cat, dog or man to obtain comparable gastric secretory stimulation. The amount of phenylbutazone administered per kilogram necessary to cause ulceration in the dog is much more than that in man [*15*]; this is probably related to the longer biologic half-life of phenylbutazone in man.

SPECIFIC ULCEROGENIC COMPOUNDS OR AGENTS

Cinchophen (Atophan). Although cinchophen is no longer used in therapy, it still remains an important ulcerogenic agent because the experimentally produced ulcer is similar to that in man. The original observations of Churchill and Van Wagoner in 1932 [*16*] of ulcer formation in dogs after the oral ingestion of cinchophen have been confirmed by many investigators [*2,17,18*]. The ulcerogenic effect of cinchophen has also been studied in cats, chickens, rats, rabbits and guinea pigs [*2*]. Only rabbits and guinea pigs seem to be resistant to ulcer formation due to the administration of cinchopen. The initial lesion simulates an erosive gastritis, with acute erosions following as a result of the digestive action of the hydrochloric acid-pepsin secretion. One or two ulcers similar in pathologic condition and location to those of chronic ulcer in man follow the gastritis which usually subsides after several weeks. Healing of the ulcers occurs promptly after discontinuing administration of the drug. The aggravation of cinchophen ulcer by vagotomy suggests that this drug may stimulate the autonomic nervous system [*19*]. Other factors postulated in the ulcer formation are disordered motility in the region of the pylorus, release of histamine, and reduction of the protective mucus barrier. The latter has been impugned as the mechanism for an increase in urinary excretion of glucuronic acid [*20*]. Serial histologic specimens of gastric mucosa obtained in dogs with a colon fistula between the stomach and abdominal wall [*17*] revealed only mild inflammatory changes during a three to four week period of daily intravenous doses of 0.1 gm. of cinchophen per kg. [*21*]. This may signify that cinchophen ulcer in the dog is due to release of histamine in the gastric mucosa. This possibility is supported by the observation that the total volume of gastric juice secreted in dogs after an injection of histamine increased twofold during the administration of cinchophen [*18*]. The administration of cinchophen alone did not increase the output of hydrochloric acid in Heidenhain and Pavlov pouch dogs, despite the development of gastric ulcer [*22*]. Magee, Kim and Ivy [*20*] noted a marked depression of gastric mucin secretion in dogs after three to four days of the administration of cinchophen.

These conflicting observations may be due to dissimilar reactions of different animals to the same drug. The results in the dog support the importance of the mucus barrier in protecting the gastric mucosa against the digestive action of gastric secretion.

Histamine. Numerous animal experiments have demonstrated the relationship between parenteral histamine injection and ulcer formation. Earlier experiments [*23*] showed that subcutaneous injection of histamine could produce acute ulceration in the rumen of the stomach of the rat. Code and Varco [*24*] introduced the incorporation of histamine in beeswax as a means of producing ulcers in animals by prolonged action of histamine. Both types of experiments suggest that the ulceration is primarily due to increased acid secretion. The vasospastic effect of histamine has been postulated as playing a contributory part in the histamine ulcer by diminishing the vitality of the mucosal cells.

The guinea pig is very susceptible while the rat is much more resistant to histamine ulceration [*2*]. This may merely be on the basis of differences in metabolic degradation or biologic half-life of the histamine and not necessarily to greater mucosal resistance. The administration of histamine alone does not cause ulceration

in the rabbit; however, the simultaneous administration of both histamine and epinephrine in beeswax results in ulceration [*25*]. In man, peptic ulcer may occur in susceptible persons treated with repeated histamine injections. Such ulceration has been reported in patients treated with histamine injection for histamine cephalalgia [*26*], multiple sclerosis [*27,28*] and Ménière's syndrome [*29*].

Caffeine. Orally or parenterally administered caffeine is a potent stimulant of gastric secretion by direct action upon the parietal cells [*30*]. Caffeine administered in beeswax produces gastroduodenal ulcers in the guinea pig [*31*] and cat [*32*]. The lesions have been ascribed to the increase of gastric secretion and lowered tissue resistance [*33*]. Caffeine does not increase gastric secretion in dogs with doses of 250 mg. of caffeine base [*30*]; the failure to stimulate gastric secretion in dogs may be due merely to insufficient dosage. Caffeine acts synergistically with histamine [*34*], resulting in prolonged and excessive stimulation of gastric hydrochloric acid secretion. It has not been proved to be ulcerogenic in man, although the occurrence of ulceration in a few patients has been preceded by the ingestion of large quantities of coffee. The fact that patients with duodenal ulcer have a marked gastric hydrochloric acid response to caffeine [*35*] suggests that excessive intake of caffeine may be a contributing factor to ulcer formation.

The evidence suggests that the mechanism for ulcer formation related to caffeine is similar to that of histamine, that is, the combination of increased gastric secretion and lowered resistance of the gastroduodenal mucosa.

Butazolidin. Butazolidin,® (1,2-diphenyl-4-butyl-3,5-pyrazolidinedione) is employed chiefly in the treatment of arthritis and musculoskeletal disorders. Its ulcerogenic properties were noted soon after its introduction in 1951 [*2*]. The experimental and clinical evidence as well as the possible mechanism of ulcer formation due to the administration of phenylbutazone have been thoroughly reviewed by Kirsner [*1*] in this country and Lambert [*2*] in France. Rats and guinea pigs are very susceptible to the ulcerogenic effect of Butazolidin; the ulceration occurs after either oral or parenteral administration and more consistently with daily than with intermittent administration. The ulceration is thought to be due to injury to the parietal cell resulting in increased susceptibility to digestion by hydrochloric acid and pepsin secretion. The prominent role of damage to the parietal cell is indicated by the observation that ulceration in the glandular part of the stomach of the rat occurs without any increase in the secretion of hydrochloric acid [*36*]. Achlorhydria may result after either oral ingestion or subcutaneous injection of this drug [*37*]. In the guinea pig a 200 mg. dose of phenylbutazone per kg. has also been noted to depress both acid and pepsin secretion and to inhibit the gastric-stimulating effect of histamine and mecholyl [*38*]. This action is considered to be due to the toxic effect of the drug upon the parietal and peptic cells. Kirsner and Ford [*39*] have reported that a single intramuscular injection of 200 to 400 mg. of phenylbutazone did not demonstrably alter the fasting gastric secretion in six dogs with various types of gastric pouches, but that single oral doses of 200 mg. did produce temporary stimulation in five of twelve such dogs. Gastroduodenal erosion and ulceration appeared in seven intact dogs who received from 3.6 to 35.2 gm. of phenylbutazone intramuscularly during a period of ten to 103 days.

The location of the Butazolidin ulcer varies in different animals [*2*]. In the rat the ulcers appeared in the glandular part and not in the duodenum or rumen; the larger ulcers at times were associated with perfuse hemorrhagic gastritis. In the guinea pig the lesions occurred throughout the stomach but not in the duodenum; in this animal the stomach seemed atonic, with dilated vessels suggesting a disturbance in the parasympathetic nervous system but no perforations were noted. The ulcerations in both the rat and guinea pig seemed more often to resemble the acute type rather than the more chronic picture observed in the dog and man.

Kirsner and Ford [*40*] found a significant increase in gastric acidity in thirty of fifty-seven subjects tested with a single oral dose of 200 to 600 mg. and in ten of thirty-two subjects tested with 50 to 400 mg. of phenylbutazone injected intramuscularly. A similar increase in gastric acidity after the administration of Butazolidin was noted in five patients with duodenal ulcer in whom vagotomy and gastroenterostomy were performed and in three of five patients in whom adrenalectomy was performed. Phenylbutazone ulceration in man usually occurs about fifteen days after the beginning of therapy and rarely with daily doses less than 400 mg. This indicates that the effective ulcerogenic dose of this drug is

much smaller in man than in animals. This is consistent with the observation that the biologic half-life of phenylbutazone is seventy-two hours in man in contrast to only six hours in the dog [*15*].

The exact incidence of ulcer due to the administration of Butazolidin is not known. Mauer [*41*] in a survey of 3,934 patients treated with Butazolidin reported forty proved cases of peptic ulcer and an additional 424 subjects with digestive symptoms including epigastric pain. Kern, Lukens and Clark [*42*] noted an incidence of 7.2 per cent of peptic ulcer among sixty-nine patients with rheumatoid arthritis who were treated with Butazolidin. There are scattered case reports of subjects with gastric and duodenal ulcers with and without perforation and bleeding following the administration of phenylbutazone [*43–45*].

From these studies it can be inferred that the administration of phenylbutazone is capable of producing multiple hemorrhages and erosions in both man and animals and that the ulceration is primarily due to a cellular toxic effect which results in lowered resistance to the digestive action of gastric juice. The observation that ulceration in man occurs usually after a few weeks of treatment, more readily in subjects susceptible to peptic ulcer, and with doses less than 400 mg. provides a therapeutic approach to the prevention and treatment of phenylbutazone ulcer. The addition of vitamin C to the phenylbutazone regimen is suggested by Aron's report that ascorbic acid plays a protective role against experimental and clinical ulceration [*46*].

ACTH and Adrenocortical Steroids. The extensive literature on the relationship between peptic ulceration and adrenocortical steroids attests to the interest in this subject. The mechanism of ulcer production during the administration of adrenal steroids is not clear. It may be related to a combination of factors, among which are increased gastric acid and pepsin secretion with increased parietal cell mass, a decrease in the mucous protective barrier or resistance of the gastric mucosa, interference with tissue repair and/or vascular and metabolic aberrations. The importance of the acid-peptic factors in steroid ulcers is emphasized by the observation that gastroduodenal ulcers occurring during the administration of adrenal steroids seem to heal with antacid treatment regardless of continuation of the steroid therapy.

The complexity of the relationship between peptic ulcer and adrenal steroid therapy is compounded by the observation that acute ulceration may occur in the absence of adrenal glands [*47*], that the gastric mucosa in Addison's disease appears to be more sensitive to the adrenal glucocorticoids than that in normal persons [*48*] and that in patients with the Cushing type of adrenocortical hyperactivity a peptic ulcer will rarely develop [*49*], although their gastric secretion is increased [*50*].

The pathways by which the effect of stress may be relayed from the hypothalamus to the stomach are considered to be neurogenic [*51*] and hormonal [*48,52*]. Physical or emotional stress is thought to activate the posterior hypothalamus with resulting increased output of ACTH by the anterior pituitary gland, followed by excessive production of adrenocortical steroids, which in turn affect the gastric mucosa. The interpretation of adrenal-stress relationship developed by Ingle and his collaborators [*53,54*] has been accepted by Engel as consistent with the results of his investigations [*55*]. According to this concept, the adrenal cortex plays a "permissive" role during stress, being necessary but not responsible for certain changes in metabolic and other functions. Selye [*56*] has continued to defend his "conditioned" theory of hormonal activity. According to this view, stress itself may "condition" the stomach to respond to adrenal hormone; many of the effects of the adaptive hormones (that is, corticoids) are largely dependent upon concurrent metabolic changes induced by stress.

There is no uniformity in the results of the investigations of the effect of steroids upon gastric secretion in man or animals. The reasons may relate to the dose and duration of the steroid administration, the age and state of nutrition and/or the degree of concomitant stress plus the many unknown factors.

An increase in gastric hydrochloric acid, pepsin and chloride has been demonstrated in intact and pouch dogs, also in vagally denervated and antrectomized dogs, following intramuscular injection of ACTH [*57*]. Increase in basal gastric secretion and secretory responses to the administration of histamine and methacholine has been reported to occur in female dogs with Heidenhain pouches after intravenous administration of prednisone [*57*]. Plainos and Philippu [*58*] have reported that the administration of 60 mg. of prednisone daily for ten days in four female dogs with a simple gastric fistula

produced a marked rise in gastric hydrochloric acid and pepsin and uropepsin secretion, both during the basal period and after histamine stimulation. The increased secretory activity persisted for a varying number of days after cessation of the administration of steroids. Clarke, Neill and Welbourn [*59*] noted that pharmacologic doses of corticotropin, cortisone, prednisone and aldosterone administered for a period of three to five days to dogs with denervated pouches produced an increase in volume and acidity, but a decrease in viscosity, pepsin activity and sodium and potassium; the chloride secretion was not affected. Cortisone also increased the maximum gastric secretory response to histamine. They ascribed the effects of these steroids as partly due to the combination of a 50 per cent increase in parietal cell population and a 36 per cent decrease in peptic cell population which was demonstrated histologically. On the other hand, Ragins and his associates [*60*] observed during a twenty-four-hour period that ACTH (40 to 80 units administered subcutaneously and intramuscularly), cortisone (200 mg. intramuscularly) or hydrocortisone (50 mg. intravenously) did not stimulate gastric volume or hydrochloric acid secretion in the isolated denervated pouches of dogs. Beck and his associates [*61*] found no appreciable change in basal secretory values except for a slight downward trend in gastric pepsin activity in three Heidenhain pouches of dogs given daily intramuscular injections of 4 mg. of prednisone per kg. during a three week period. In pylorus-ligated rats, Welbourn and Code [*62*] observed, with one exception, no significant rise in gastric acidity or increased frequency of ulcers in the rumen of the stomach of the rat after intramuscular injection of cortisone (20 mg. daily for three to seven days). However, the Shay rat is not a suitable animal to use for testing increased gastric secretion since maximum secretion usually occurs merely as a result of ligating the pylorus.

In man, corticotropic hormones must be administered in large doses (100 to 160 units daily) for three to four weeks or longer to produce a significant elevation in the output of hydrochloric acid and pepsin [*48*]. The short term administration of corticotropin or glucocorticoids for periods of three to ten days increased the acid and pepsin secretions in only four of seventeen subjects [*48*]. Carbone, Liebowitz and Forsham [*63*] observed an elevation in the one hour basal secretion in normal young men given 40 mg. of prednisone daily for one week. The response was inhibited by an anticholinergic drug. Kirsner [*1*] reported that the administration of single average doses of corticotropin intramuscularly or cortisone orally did not stimulate gastric secretion in man. In two subjects with gastric ulcers the basal secretion rose during the use of ACTH; in three other patients with an ulcer the gastric response to the administration of histamine was unchanged after several weeks of corticotropic therapy; in eleven patients with ulcer or ulcer-like symptoms the one hour basal secretion remained normal or low during steroid therapy; in nine of ten patients with ulcerative colitis given large doses of ACTH, hydrocortisone or prednisone the pattern of the two hour basal secretion did not show a significant rise during an observation period up to sixty weeks. Dreiling and Janowitz [*64*] found no change in gastric secretory volume, acid or pepsin output in normal persons or in patients with gastric or duodenal ulcer given ACTH, hydrocortisone or prednisolone intravenously. Hirschowitz and his associates [*65*] in a study of the eight hour gastric response of normal subjects to the administration of ACTH, hydrocortisone, corticosterone, prednisone and aldosterone observed a slight rise in gastric juice, a decrease in visible mucus and viscosity of gastric contents with no change in the plasma pepsinogen but with a striking increase in uropepsin activity. Kammerer and Rivelis [*66*] noted that hydrocortisone, prednisone or prednisolone given orally for five or more days did not significantly increase the output of hydrochloric acid or pepsin in patients with rheumatoid arthritis, even in those patients in whom an active ulcer had developed; there was a slight decrease in the viscosity of the gastric juice and an appreciable increase in uropepsin activity. Beck and his group [*61*] in a study of twelve healthy young male students observed no change in gastric hydrochloric acid and blood pepsinogen during a twenty-four day period of daily administration of 15 to 20 mg. of prednisone. A significant rise in the concentration of gastric pepsin occurred only at the end of the third week of treatment and in uropepsin only at the end of the first week; only one weekly determination was made in these studies. In the group receiving 30 mg. of prednisone daily for seven days there was no change in the secretion of gastric acid and only an insignificant increase in blood and urinary pepsinogen.

These data indicate some variability in the gastric hydrochloric acid and pepsinogen secretory response to ACTH and adrenocortical steroids. Consistency in response has been noted in the decrease of viscosity of the gastric juice and in the elevation of uropepsin activity; the latter may merely denote an increase in the renal clearance of plasma pepsinogen.

Regardless of the observed effects of corticotropin and adrenocortical steroids on gastric secretory activity, the important question is whether or not new peptic ulcers form or old peptic ulcers are reactivated by the administration of steroids. In this evaluation, consideration must be given to the dose and duration of therapy and to the effect of previous medication with ulcerogenic drugs, as well as to the natural incidence of peptic ulcer in the disease treated.

In two separate series collected by Gray, of 1,343 [*67a*] and 1,361 [*67b*] patients treated with ACTH or the adrenocortical steroids, the average incidence of peptic ulcer was 6.3 and 7.1 per cent, respectively. The range of incidence varied from 1.2 to 24 per cent depending upon the dosage and duration of steroids administered. Meltzer et al. [*68*] reported a 3.6 per cent incidence of fresh peptic ulcer in a group of fifty-five patients (twenty-two white and thirty-three Negro) who received an average daily dose of 13.8 mg. of prednisone during a period of 11.2 months; these persons had no previous history of ulcer. There was no change in the incidence of ulcer of 10 per cent in another series of 60 subjects (thirty white and thirty Negro); these patients had a previous history of ulcer and were treated with an average daily dose of 14.2 mg. of prednisone for about fifty-two months. Most of these patients had rheumatoid arthritis. The authors concluded from these data that the administration of prednisone in daily doses approximating 14 mg. is not ulcerogenic. Clark and his group [*69*] did not find a single case of peptic ulcer among seventy-six and sixty patients with rheumatoid arthritis, respectively, treated with ACTH or cortisone.

On the other hand, Edgecomb [*70*] reported an ulcer incidence of 27 per cent in 48 rheumatoid arthritic patients after four to 109 weeks of steroid therapy. Hilbish and Black [*71*] noted twelve peptic ulcers among forty-nine rheumatoid arthritic patients (incidence 24 per cent) who received more than 15 mg. of prednisone during a period ranging from four weeks to six years. Gedda and Moritz [*72*] found the frequency of ulcer in a group of rheumatoid arthritic patients on steroid therapy to vary from 4 to 26 per cent. Kammerer, Freiberger and Rivelis [*73*], in a comparison of the results of gastrointestinal series in three groups of patients (117 with rheumatoid arthritis treated with average daily doses of 10 to 15 mg. of prednisone, thirty-three untreated patients with rheumatoid arthritis and thirty-seven miscellaneous subjects with orthopedic disorders of comparable ages), found an ulcer incidence of 31 per cent in the treated rheumatoid arthritic group compared to 9 per cent in the untreated group and a questionable 5 per cent in the orthopedic group. The ratio of gastric ulcer to duodenal ulcer in the steroid treated group was 6 to 1; twenty-one of the patients with roentgenographic evidence of peptic ulcer had no symptoms.

Paraphrasing Gray [*48*] in the evaluation of the causal relationship between peptic ulcer and steroid therapy, the incidence of fresh peptic ulcer occurring in patients receiving steroids should be compared with the general incidence in a similar population during a period of time comparable to that of the administration of steroids. The steroid-associated incidence should not be compared with the general incidence of peptic ulcer, which is reported to be from 5 to 10 per cent [*11*]. Since fresh ulcers in patients on a steroid regimen usually appear within months of steroid therapy, the per annum incidence of non-steroid associated ulcers should serve as a basis for this evaluation. A six year survey (1952 to 1957) of the incidence of new cases of peptic ulcer in the City of York, England [*74*] revealed that the mean annual incidence of duodenal and gastric ulcer was 0.24 and 0.062 per cent, respectively. Sponheim [*75*] reported that the per annum incidence of new ulcer cases among patients seeking medical care in a Norwegian county during a two and a half year period (January 1, 1950 to July 1, 1952) was 0.26 per cent. Unfortunately, this survey did not include the occurrence of ulcers among patients who did not apply for medical care. The fact that the average incidence of peptic ulcer among the steroid-treated groups collected by Gray [*67*] approximated 7 per cent indicates that there is a significant causal relationship between peptic ulcer and steroid therapy. The rheumatoid arthritic group may require special consideration, since the incidence of peptic ulcer in rheumatoid arthritic patients before the steroid era has been reported to average 4.5 per cent

[*76*]. However, the incidence of peptic ulcer in the steroid-treated rheumatoid arthritic group averaged more than 4.5 per cent in the literature reviewed.

There is also conflicting evidence relative to the effect of ACTH and adrenocortical steroids on the healing of peptic ulcer. Sandweiss, Scheinberg and Salztein [*77*] have reported favorable therapeutic results with ACTH and cortisone in dogs with Mann-Williamson's operation. Experiments in mice have shown that the administration of prednisone did not delay the healing of gastric mucosal and serosal wounds [*78*]. There are also observations [*79*] that the administration of cortisone interferes with the healing of duodenal ulcers but not with that of gastric lesions. The studies of Hirschowitz and coworkers [*80*] imply that administration of the steroids lessens the protection of the mucosa against the digestive action of the gastric juice as a result of a decrease in the mucous barrier. Diminished tissue resistance as a consequence of steroid therapy is suggested by the observation [*81*] that ACTH and cortisone administration in rabbits increased the depth of pitressin gastric ulcers, although these steroids alone failed to produce lesions. Kirsner, Klotz and Palmer [*82*] have described the unfavorable course of ulcer in three patients receiving ACTH or cortisone.

A recent report [*83*] suggests that the administration of triamcinolone may not be as ulcerogenic as the other steroids. This conclusion was based both on the disappearance of the ulcer crater in one patient on prednisone therapy after changing the treatment to a daily dose of 4 to 12 mg. of triamcinolone and the observation that twenty-three other patients with various allergic diseases treated daily with triamcinolone for forty-six to 114 weeks gave no evidence of peptic ulcer; this was demonstrated by repeated gastrointestinal series. Since only one observation has little value and since patients with asthma and ulcerative colitis have a lower incidence of peptic ulcer with steroid therapy than other similarly treated groups, further observations are necessary before any significance can be attached to this study.

Salicylates. Salicylates have long been implicated as the cause of epigastric pain, gastric hemorrhage and ulceration [*84–89*]. Investigations with animals dating from 1904 to 1958 relative to the effect of salicylates upon gastric secretion and the gastric mucosa have been reviewed by Lambert [*2*]. Schnedorf, Bradley and Ivy [*90*] observed that prolonged daily administration of aspirin in normal dogs and dogs with Heidenhain pouches resulted in augmentation of gastric secretion. The observation that 70 to 95 mg. of aspirin per kg. during a five day period failed to increase the gastric secretion in Cope pouch dogs while doubling these doses enhanced the gastric secretion suggests that the gastric secretory response may depend upon the dose of salicylate [*91*]. A decrease in gastric acidity was noted in five of thirty-five Shay rats after the oral administration of 2.5 gm. of aspirin [*92*].

Schnedorf and his group [*90*] in clinical experiments observed an increase in the total titratable acidity after the ingestion of 1 to 2 gm. of aspirin. Muir and Cossar [*86*] also noted an increase in gastric secretion with large doses of salicylates. Gompertz and his associates [*93*] found no statistically significant change in basal secretion except for increased volume following prolonged administration of acetylsalicylic acid in a comatose patient. Rubin, Pelikan and Kensler [*94*], by the employment of a continuously recording glass electrode placed in the stomach cavity, found that the gastric secretory response to buffered or unbuffered aspirin did not differ significantly from water alone.

Hyperemia, ecchymosis and ulceration of the gastric mucosa have been noted in animals after either oral or parenteral administration of salicylates. Daily oral or subcutaneous administration of 300 mg. of acetylsalicylic acid per kg. for a period of ten days produced acute superficial ulceration in the glandular part of the stomach of the rat [*95*]. Healing occurred within ten days after the cessation of administration of the drug. Ulceration has also appeared in dogs and guinea pigs after oral ingestion of aspirin [*2*].

Douthwaite and Lintott [*96*] on the basis of gastroscopic examinations concluded that salicylates can produce gastric hemorrhage as a result of gastric mucosal irritation in the lower part of the stomach. Their observations were not confirmed by Paul [*97*] who observed no mucosal changes after the ingestion of aspirin in a series of 107 normal patients examined gastroscopically. The aspirin tablets in this group were located usually in or near the mucous lake. Muir and Cossar [*98*] believe that the bleeding due to the ingestion of aspirin is associated with acute gastritis produced by local irritation of the aspirin particles; they imply that the conclusions

of Paul and the other authors who disagree with the contention that aspirin causes gastric irritation are invalid. Muir and Cossar [*98*] also noted that fifty-seven of a group of 106 patients with gastrointestinal hemorrhage had ingested aspirin within forty-eight hours of their hemorrhage, in contrast to seventeen patients of a control series of 106 patients without hemorrhage who had taken aspirin within forty-eight hours of their hospital admissions. Brown and Mitchell [*99*] reported that hemorrhage in 70 per cent of patients with duodenal ulcer was related to the use of salicylates for headache, arthritis and upper respiratory infection and that perforation of peptic ulcer in seven of nine patients had been preceded by ingestion of salicylates. Stubbé [*100*] reported that 70 per cent of 140 patients with rheumatic disease and 70 per cent of forty healthy control subjects who took aspirin had occult blood in the stools. The bleeding was unrelated to the dyspepsia regardless of dose or route of administration of the drug. Lange's studies [*101*] also suggested that the ingestion of salicylates is a significant factor in provoking gastric hemorrhage. Matsumoto and Grossman [*89*] noted, by means of the injection of red blood cells tagged with Cr^{51}, an increased loss of fecal blood after the ingestion of 3 gm. of aspirin daily for three to six days. With a similar technic, Porter, Lewis and Dixon [*102*] demonstrated a slight daily blood loss in eleven subjects taking either aspirin or calcium aspirin. The amount of blood loss decreased or disappeared in the patients given enteric-coated sodium salicylate. Levy and Hayes [*103*], in a study on the physiochemical basis of the buffered acetylsalicylic acid controversy, have concluded that serious gastric mucosal irritation and delayed aspirin absorption occur when acetylsalicylic acid is swallowed as whole tablets. Minimal local irritation can be expected only if the drug is given in solution as a fine powder with enough water after meals, when the gastric mucosa is protected by food. On the other hand, Baragar and Duthie [*87*] in a study of 244 patients with rheumatoid arthritis followed for about six years, concluded that the majority of patients with rheumatoid arthritis can tolerate aspirin without an increase in anemia; this suggests that minimal blood loss due to aspirin is of minor importance as the cause of anemia in patients with rheumatoid arthritis. They noted clinical or radiologic evidence of peptic ulcer in ten of these patients (4 per cent); in only three patients (1.2 per cent) an ulcer developed during the period of observation.

The possibility that the effect of salicylate upon the gastric mucosa may not be completely explained by its local action has prompted the investigation of an indirect pathway of action. Smith [*106*] has reviewed the evidence supporting the hypothesis that salicylate in rheumatic fever stimulates the pituitary-adrenal system. However, urinary excretion of adrenocortical steroids in patients receiving salicylates was not found to be increased [*104*]. Similarly, the adrenal response as measured by plasma level of 17-hydroxycorticosteroids also suggests that salicylates (in doses of 1.3 to 2 gm. four times a day) do not stimulate the pituitary-adrenal system [*105*].

The data reviewed support the hypothesis that acetylsalicylic acid, especially in non-soluble form, can produce local gastric mucosal irritation with resulting blood loss. Thus it would seem advisable to administer salicylates, as recommended by Levy and Hayes [*103*], either in a dilute solution after meals or in the enteric-coated form.

Reserpine. Reserpine is now widely used in the therapy of hypertension and certain emotional disorders. Reports of the occurrence of digestive disturbances [*2*] and peptic ulcer [*107,108*] during its administration have prompted investigation of its effect upon gastric secretion and ulcer formation.

Barrett and his group [*109*] reported stimulation of gastric secretion with the administration of reserpine both in normal dogs and in dogs with Heidenhain pouches; the secretory effect was not dependent upon an intact vagus. In man, intravenously administered reserpine stimulates basal gastric secretion within thirty minutes; the effect lasts at least four hours [*110*]. The observation that this secretory response is not inhibited by anticholinergic drugs, epinephrine or antihistamine [*111,112*] or by vagotomy or a combination of vagotomy and sympathectomy [*113*] suggests a humoral or peripheral action. The administration of single 5 mg. intramuscular injections of reserpine has been found to increase the gastric volume and the output of hydrochloric acid; the gastric volume response is lessened while the concentration of hydrochloric acid is not affected by the administration of 1 mg. of atropine prior to the reserpine injection [*114*]. Haverback et al.

have reported an increase in the output of hydrochloric acid after oral administration of 1 to 1.5 mg. of reserpine [*115*]. On the other hand, Schneider and Clark [*116*] did not observe increased gastric secretion with a single oral dose of 1 mg. of reserpine but noted a significant rise after oral administration of 2.5 mg. Kirsner and Ford [*117*] have reported that the daily oral administration of 1 mg. of reserpine did not increase the basal gastric secretion in seven of eight subjects, while 1 to 2.5 mg. of reserpine injected intravenously produced a marked stimulation.

The role of the adrenal cortex in the action of reserpine remains unsettled. Large amounts (5 mg.) of reserpine injected intravenously in dogs produced an increase in 17-hydroxycorticosteroids [*118*]. Anderson [*119*] observed an increased excretion of 17-ketosteroids in three monkeys maintained on reserpine for nine days, a striking decrease in eosinophils in normal dogs but not in the hypophysectomized animal, and a greater response to a test dose of ACTH in children treated with reserpine. These findings suggested to him that reserpine can activate the ACTH-steroid release mechanism.

Benditt and Wong [*120*] noted acute gastric hemorrhage with superficial mucosal ulceration of the glandular part of the stomach of the rat after administration of 5 mg. per kg. of reserpine. They also observed an 80 per cent decrease in the number of visible argentaffin cells in the stomach of rabbits and the duodenum of guinea pigs sixteen hours after the injection of 5 mg. of reserpine per kg. The opinion that the ulcerogenic effect of reserpine therapy is attributable to a release of serotonin and/or histamine is fortified by the observation of mucosal erosion occurring in the glandular part of the stomach of the rat after the administration of the serotonin precursor, 5-hydroxytryptophan [*121*]. Waalkes and Weissbach [*122*] have reported a release of serotonin from the platelets of rabbits as well as the release of histamine after the intravenous injection of reserpine. Blackman, Campion and Fastier [*123*] have stated that the administration of reserpine-like drugs cause gastric hemorrhage by a mechanism which involves the liberation of 5-hydroxytryptamine. The observation that this did not occur in vagotomized mice or in mice receiving iproniazid suggests that a central component is involved.

These data indicate that the action of reserpine may be due either to a direct effect upon the gastric mucosal cells or to an indirect result by the liberation of serotonin and/or histamine, or to the activation of the ACTH steroid release mechanism or a combination of these factors.

Although gastrointestinal hemorrhage, peptic ulceration and perforation have been reported during the administration of reserpine [*107,108, 122,124*], the exact incidence of these complications can not be estimated. From the data presented, it seems that the oral administration of reserpine in doses up to 1 mg. daily may be without much risk of producing or reactivating a peptic ulcer. Larger doses administered orally or intramuscularly would seem contraindicated, especially in patients with suggested or known history of peptic ulcer.

CONCLUDING REMARKS

Although the fundamental cause of peptic ulcer in man is unknown, two factors appear to be of paramount importance, namely, the combination of hydrochloric acid and proteolytic enzymes (pepsin and/or cathepsin) and lowered resistance of the gastroduodenal mucosa to the digestive action of the gastric juice. The ascendancy of either one of these components in ulcer formation depends directly upon the drug's predominant action or indirectly upon the gastric secretory mechanism or upon those elements providing normal resistance to digestion. The latter may be contingent upon the state of the gastroduodenal vascular system, the protective mucous barrier, the regenerative capacity of the mucosal cells and the activity of the intracellular enzyme system.

In man, the causal relationship of ulceration to a specific drug, although suspected, can not always be established with certainty. Confirmation of the ulcerogenic potentiality by animal experiments, the early chronological association of medication to development of the ulcer, and comparison of the incidence of fresh ulceration during therapy with that in a comparable population during a period of time approximating that of administration of the drug may be very suggestive but not necessarily conclusive in an individual case. Other circumstantial factors requiring consideration are the individual susceptibility to ulcer, the incidence of peptic ulcer in the disease treated, emotional disturbances and the preceding or concurrent administration of other ulcerogenic drugs.

Irrespective of all this, it is evident from the

data presented that certain drugs have ulcerogenic properties due to one or more of the factors described. Excessive gastric secretion, regardless of the mechanism of its production, predominates in ulcer formation by histamine, caffeine and reserpine. Other mechanisms may be contributory, such as vasospasm in the case of histamine ulcer and vascular congestion and mucosal irritation with caffeine. Diminished tissue resistance is conspicuous in the development of ulceration as a result of cinchophen, phenylbutazone or salicylate administration. Cinchophen and phenylbutazone produce a severe erosive gastritis primarily as a result of their toxic effect upon the gastric mucosa. Reduction of mucus secretion, disordered motility and increased acidity secondary to irritation of the parietal cells or histamine release may play a temporary contributory part in the development of cinchophen ulcer. The gastritis and bleeding supposedly associated with salicylate ingestion is considered to be due to the local irritative action of particles of acetylsalicylic acid. There is no consistent evidence that salicylates increase gastric secretion either by a direct effect or by way of the pituitary-adrenal system.

The relationship between peptic ulcer and the administration of ACTH and adrenocortical steroids is rather complex. This is understandable in the light of the complex functions of adrenal steroids in stress. One or more of the various factors assigned a role in ulcer development during the administration of steroids are augmented acid-pepsin secretion, diminution of the protective mucous barrier, decrease of mucosal resistance and interference with healing as well as the possibility of vascular and metabolic aberrations. Experimental observations suggest that excessive output of gastric hydrochloric acid is not usually predominant in the development of steroid ulcer. The importance of diminished tissue resistance in steroid-ulcer formation is connoted by the high proportion of gastric ulcers, the decrease in the protective mucous barrier, delayed healing and the greater incidence of perforation, as well as occasional perforation elsewhere in the digestive tract.

Awareness of the ulcer potential of any medication should aid in the proper management of a patient receiving such a drug; it should also contribute to the prevention of complications and to the healing of an ulcer already present. Effective neutralization of gastric acidity by diet, antacids and anticholinergic drugs should be instituted when the use of an ulcerogenic drug appears unavoidable. It is fortunate that drug-induced or drug-associated ulceration usually responds promptly to adequate antacid therapy, especially when administration of the drug is discontinued.

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Treatment of Peptic Ulcer*

Current Concepts

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EXCLUDING the many new remedies of transient interest or of no value, there have not been any significant modifications in the principles of ulcer therapy in recent years. Currently, there appear to be at least four trends in therapy, in addition to the "standard" approach: (1) the rejection of all forms of treatment, based upon the philosophy that peptic ulcer pursues an independent course uninfluenced by identifiable circumstances or known treatment; (2) therapeutic liberalism, emphasizing the lack of objective evidence for the value of diet and antacids; (3) the psychiatric concept of the genesis of peptic ulcer, attributing the results of medical treatment to subtle psychogenic influences rather than to pharmacologic effects and (4) the organic concept of peptic ulcer, but with extremely speculative causes, including alleged deficiencies of "healing substances" in animal tissues, in the serum and urine of patients with ulcers, cabbage juice, hormones, mineral springs and soy beans. These and other theories, challenging established methods of treatment, yet themselves lacking significant supporting evidence, contribute to the present confusion and uncertainty in the management of peptic ulcer.

Although the fundamental cause of peptic ulcer remains obscure, much is known of its pathogenesis and course [*1–3*]. Physiologically, peptic ulcer is characterized by failure of localized areas of the gastroduodenal mucosa to withstand the digestive action of acid-pepsin gastric juice. Hypersecretion predominates in duodenal ulcer; decreased tissue resistance seems to be the major factor in gastric ulcer. However, the presence of hydrochloric acid is indispensable to the development of all chronic benign peptic ulcers: esophageal, gastric, duodenal, "endocrine-influenced" and "drug-induced." The occurrence of peptic ulcer only among individuals capable of secreting hydrochloric acid; its location in only those areas of the digestive tract exposed to the acid; the presence of hydrochloric acid in *all* chronic benign peptic ulcers when tested adequately; the cure of peptic ulcers following complete elimination of hydrochloric acid; the healing of the otherwise refractory "endocrine ulcer" after total gastrectomy; and, finally, the dependence of experimentally induced peptic ulcer upon either the overproduction of acid or interference with the normal mechanisms for neutralizing and buffering the acid; all these established clinical and experimental facts reaffirm the indispensable role of hydrochloric acid in the pathogenesis of peptic ulcer in man. Tissue vulnerability, localized or diffuse, should be an important etiologic factor, perhaps in determining individual susceptibility. However, little or no information is available on the nature of tissue resistance in peptic ulcer. More information is needed on the rate of regeneration of epithelial cells of the mucosa, the mucus cells and the mucoid constituents of the gastric content and the vascularity of the stomach and duodenum. The biochemical characteristics of the gastroduodenal epithelium, intracellular enzymes and the role of genetic influences also require further investigation.

In the absence of an established cause, the treatment of peptic ulcer continues to emphasize protection of the gastroduodenal mucosa from the digestive action of hydrochloric acid and pepsin [*4–6*]. This objective probably would be accomplished by increasing tissue resistance, without altering gastric secretion. However, satisfactory methods for directly improving the defenses of the stomach and duodenum have not become available. The complete and permanent elimination of hydrochloric acid would abolish peptic ulcer, regardless of tissue susceptibility and other etiologic factors; but no procedure, except total gastrectomy, consistently produces complete anacidity. Despite these limitations,

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comprehensive medical therapy facilitates healing and reduces the frequency of complications and recurrences. The purpose of this paper is to review the present medical management of peptic ulcer in relation to the foregoing observations.

Diet. There is no evidence relating the usual peptic ulcer to abnormal protein metabolism or to nutritional deficiency. Consequently, there is no scientific rationale for unusual preparations incorporating animal tissue extracts with food supplements. Decreased intake of food as a result of poor appetite or restricted diet and chronic loss of blood via the gastrointestinal tract may cause a relative deficiency of protein, necessitating increased intakes of nitrogen [*7*]. Protein-vitamin-mineral supplements provide additional calories and proteins; however, they are not indicated when the intake and digestion of food are normal.

There is no conclusive proof that coarse or highly seasoned foods are directly irritating to an ulcer or that the maintenance of a soft diet increases the rate of healing [*8,9*]. However, attempts to evaluate the role of diet in short term surveys or isolated from other components of the total therapeutic program probably do not permit a representative appraisal. The patient with an ulcer is capable of eating a more liberal diet than has been advocated in the past and dietary restrictions do not uniformly cure peptic ulcer. However, the experience of the intelligent patient consistently implicating certain foods in the persistence or intensification of pain is not without importance, and this information provides a useful means of relieving distress. The most practical approach, in our experience, is to avoid the extremes of rigid restriction and nutritional nihilism.

Foods stimulate gastric secretion by neurogenic, chemical, mechanical and humoral mechanisms. All foods may increase gastric acidity and pepsin output but some are more stimulating than others. Meat, fish and eggs increase gastric secretion. Fruits, vegetables and foods rich in carbohydrates evoke a lesser secretory response. Efforts to lower gastric secretion by food presumably would involve a diet low in protein and high in carbohydrate and fat but there are practical and theoretic objections to this type of regimen. Milk, a traditional mainstay of the ulcer diet, does not decrease gastric acidity.

Dietary management involves frequent feedings of bland foods, providing an adequate intake of proteins, carbohydrates, calories, minerals and vitamins and facilitating the neutralization and buffering of the gastric content. The diet usually includes milk and cream which is taken hourly or every two hours. In the absence of gastric retention, additional foods are administered as feedings. With complete relief of ulcer distress, a bland diet of three meals is prescribed, supplemented by a feeding later in the evening. All foods should be well cooked and chewed thoroughly; they need not be pureed. The selection of palatable foods prepared attractively, regular eating habits and physical and emotional relaxation at the time of eating are important considerations. Coffee and tea are permitted in moderation. The "bland" three meal diet is continued indefinitely, with additions as indicated by the progress of the patient. The dietary program should be described clearly to the patient, preferably in a printed list. The casual suggestion to "watch your diet" or "avoid irritating foods" is ineffectual and should be avoided.

The standard diet in an ulcer condition seems to be high in saturated fats and relatively low in unsaturated fats [*10*]. Opinions differ as to the possible relationship between the usual diet prescribed because of ulcer, arteriosclerosis and coronary artery disease. In our experience the incidence of arteriosclerosis and coronary artery disease has not been excessive among patients with peptic ulcer. Other observers have reported such a correlation. A decrease in the caloric and fat content of the diet probably is desirable in the obese patient and in individuals with elevated blood cholesterol; perhaps the diet should be low in saturated fatty acids and high in polyunsaturated fatty acids [*10*].

Antacids. The purpose of antacid therapy is constant neutralization of the continuously secreted acid gastric content. The ideal antacid should possess these advantages: prolonged, effective neutralization when administered orally in acceptable amounts, no untoward systemic effects such as alkalosis, no cathartic or constipating action, no interference with digestive or absorptive processes, palatability and low cost. Ideal neutralization is maintenance of the pH of the gastric content between 4.0 and 5.0 or higher; at this hydrogen ion concentration, acid and peptic activity are practically absent. On the other hand, peptic ulcer may heal with less complete control of gastric acidity. Antacids cannot be selected for clinical use solely on the

basis of in vitro neutralizing capacity because laboratory conditions cannot reproduce the secretory activity of the human stomach. Neutralizing efficiency in patients with peptic ulcer is limited by the excessive gastric secretion and by the rate of gastric emptying. There is no acceptable evidence for "acid rebound" after antacid therapy.

The ideal antacid preparation thus far has not been developed. The most potent compound probably is calcium carbonate, administered in quantities of 2 to 4 gm. hourly during the day and evening. The neutralizing effect is enhanced by the simultaneous administration of atropine sulfate, anticholinergic compounds or by 5 ml. oleic acid, prolonging the emptying of the stomach [*11*]. Dosages of 8 gm. of calcium carbonate are not more effective than 4 gm. The principal disadvantage of calcium carbonate is constipation especially in older patients; this usually can be corrected by substitution of magnesium carbonate in amounts required by the individual patient. Therapy with milk and calcium carbonate may be complicated infrequently by the hypercalcemic syndrome. This disorder is characterized clinically by weakness, headache, distaste for food, nausea and vomiting. The chemical features are elevation of the serum calcium and blood urea nitrogen and temporarily depressed renal function. This complication is more likely to occur in older patients with hypertension and pre-existing impairment of renal function or when renal function is disturbed by gastrointestinal hemorrhage or electrolyte and fluid depletion. It also has been observed in patients taking milk and cream and sodium bicarbonate. The syndrome subsides rapidly after discontinuance of milk and alkali and the intravenous administration of isotonic sodium chloride solution. In some instances the discontinuance of milk alone, continuing the calcium carbonate, has permitted restoration of normal electrolyte balance.

Combinations of calcium carbonate with glycine or calcium caseinate do not offer additional neutralizing advantages. Magnesium carbonate and magnesium oxide are potent antacids; because of their laxative effect, they are prescribed chiefly to counteract the constipating action of the ulcer regimen. Tribasic calcium phosphate, tribasic magnesium phosphate, magnesium trisilicate, magnesium hydroxide, magnesium tartrate, calcium tartrate and dihydroxyaluminum sodium carbonate, in doses of 2 to 4 gm. hourly, neutralize gastric acidity in varying degrees. Aluminum hydroxide, aluminum phosphate and basic aluminum carbonate, alone in doses of 8 to 16 cc. and in various mixtures, partially neutralize gastric acidity. Their capacity to inactivate pepsin in vivo seems no greater than that of calcium carbonate; their alleged astringent, demulcent and coating properties have not been demonstrated objectively; nor are these effects necessarily beneficial. Aluminum hydroxide increases the excretion of phosphate in the feces; however, the serum electrolytes are not altered. Hydrated sodium aluminum silicate, "non-reactive" aluminum hydroxide and dihydroxyaluminum aminoacetate do not offer any advantages.

Anion exchange resins, such as polyaminemethylene resin, are large insoluble bases with the capacity to absorb the anion of an acid forming an insoluble resin salt. In the alkaline intestinal contents the anion exchange is reversed and the resin is restored to its original state. Various resins, alone or in combination with antacids, may lower gastric acidity partially in man. Bismuth salts, hog gastric mucin, protein hydrolysates and sodium carboxymethylcellulose, alone or in combination, are ineffective. The antacid effect of sodium bicarbonate is pronounced but transient.

Antacid tablets contain aluminum hydroxide, magnesium trisilicate, calcium carbonate, magnesium oxide or magnesium carbonate, alone, in various quantities and mixtures, or combined with resins, milk proteins and vitamins. Such preparations are inferior to powdered or liquid antacids because of the smaller amounts entering into the reaction with hydrochloric acid. Their principal indication may be as adjunct medication taken away from home and their usefulness depends upon adequate dosage.

Gastric acidity also may be neutralized by the continuous administration of milk and cream, alkali or food supplements, administered through an intragastric tube. The drip may be maintained for the twelve hour night period or continuously for several days. This procedure has been utilized in patients with gastric hypersecretion and severe pain not responding to ordinary measures and occasionally in the treatment of massive hemorrhage; it is contraindicated in the presence of pyloric obstruction. The intragastric drip is not practical for general or prolonged use.

Antacids act locally upon the gastric contents. Since they do not influence the acid-secreting cells of the gastric secretory mechanism, their neutralizing effect is temporary and disappears when medication is discontinued. Antacid requirements in peptic ulcer are high; the dosage, therefore, should be sufficiently large and preferably determined in the individual patient. Since ulcers recur, therapy must be prolonged. The administration of small quantities of mild antacids immediately after meals or "as needed" is impractical and ineffective since the food alone neutralizes acid during this period; and the subsequent intervals between medication are too long for continuous control of gastric acidity. If antacids are prescribed only occasionally, they are more useful several hours after meals when the buffering effect of food has been dissipated. An obvious defect of antacid therapy is inability to neutralize the excessive nocturnal gastric secretion of duodenal ulcer unless prescribed during the night.

Gastric Antisecretory Compounds. Anticholinergic drugs interfere with the transmission of nerve impulses mediated by acetylcholine at the neuro-effector junctions of postganglionic cholinergic nerves. Interest in anticholinergic medication has been based upon the theoretic possibility of prolonged suppression of acid secretion, permitting a more liberal yet effective antisecretory program, and upon the concept that parasympathetic (vagal) hyperactivity is chiefly responsible for the gastric hypersecretion of duodenal ulcer. Other phases of gastric secretion, including the antral mechanism and the parietal cells, also are influenced by these agents. Most anticholinergic drugs decrease gastrointestinal motility and diminish muscle spasm; however, this effect is not essential to the healing of peptic ulcer. Anticholinergic drugs do not mask the symptoms of perforation.

Average doses of tincture or powdered extract of belladonna do not inhibit acid secretion significantly in patients with peptic ulcer. Atropine sulfate, 0.5 mg. given orally three or four times daily, is partially inhibitory; the same dosage intramuscularly is more effective. The chief usefulness of atropine and similar compounds in ulcer therapy may be to delay gastric emptying, permitting a longer period of interaction between acid and antacids. Synthetic atropine substitutes, including amprotropine phosphate, homatropine methylbromide, adiphenine hydrochloride, dibutoline sulfate and dicyclomine hydrochloride, are less potent than atropine. The quaternary ammonium compounds, tetraethylammonium chloride or tetraethylammonium bromide, administered parenterally, and hexamethonium salts, prescribed orally, may inhibit hydrochloric acid temporarily. However, these drugs cause disturbing side effects, including postural hypotension and intestinal atony and they are not intended for use in ulcer therapy. Recently, a new quaternary ammonium derivative of atropine, propionyl atropine methyl nitrate, has been reported favorably [*12*].

Methantheline bromide and diphemanil methylsulfate are slightly more inhibitory, especially when injected intramuscularly but their effects are not impressive. More than 100 gastric antisecretory compounds have been developed in the past ten years including: benzomethamine chloride, clidinium bromide, hexocyclium methylsulfate, homatropine methylbromide, methscopolamine bromide, methscopolamine nitrate, oxyphenonium bromide, penthienate bromide, pipenzolate methylbromide, piperphenamine bromide, propantheline bromide, tricyclamol methylsulfate, tridihexethyl iodide and others [*13,14,15*].

Anticholinergic compounds are more potent when administered intramuscularly than orally, but parenteral therapy, except in occasional hospitalized patients, is not practical. Since they are more effective against basal than against food-stimulated secretion, the medication is taken before meals. Increased amounts, two or three times larger than average, are prescribed at bedtime in an effort to lower the nocturnal gastric secretion. Since the action of these drugs is limited to the period of administration, they must be taken continuously; however, patients occasionally appear to develop a tolerance to this medication. The important considerations in anticholinergic therapy are sufficient quantities and sustained administration. The most useful clinical guide as to adequate dosage probably is the occurrence of dryness of the mouth.

No single anticholinergic compound excels in gastric inhibitory capacity, clinical tolerance and therapeutic value. In general, the drugs that lower acidity most effectively also produce systemic manifestations of parasympathetic inhibition. The gastric antisecretory effects of coated or delayed action anticholinergic preparations, such as oxyphencyclimine hydrochloride and N-ethyl-3-piperidyl diphenylacetate hydro-

chloride, although demonstrable [*16*], may be uncertain. The combination of anticholinergic drugs with tranquilizers does not offer any advantages justifying the added cost [*17*].

The ideal gastric antisecretory agent suppressing acidity for long periods after oral administration, without development of tolerance and with minimal or no side effects, thus remains to be synthesized. Present compounds do not produce a true "medical vagotomy." However, they are superior to belladonna, atropine, methantheline and diphemanil. Several preparations, administered orally, may decrease acid secretion at least temporarily. As adjuncts to antacids, in sufficient amounts, they probably facilitate more efficient neutralization of the gastric content. In occasional patients, at least, they may benefit not only the immediate response but also the long term course of peptic ulcer. Their value in preventing the complications of peptic ulcer and in decreasing the need for surgery has not been established. In general, the therapeutic effects of anticholinergic drugs in the long term management of peptic ulcer have been disappointing, perhaps because of inadequate dosage, insufficient to control gastric acidity completely. The use of anticholinergic drugs alone in the management of peptic ulcer, therefore, is not recommended. These compounds are contraindicated in the presence of pyloric obstruction, incipient glaucoma, prostatic hypertrophy and cardiospasm.

Gastric Aspiration. Nightly aspiration of the stomach, now performed infrequently, is useful in hospitalized patients with gastric retention, since it removes a considerable quantity of acid gastric content otherwise bathing the ulcer and contributing to its chronicity. Gastric aspiration is very effective in relieving severe ulcer pain not responding to antacids. The procedure also provides useful information regarding continued medical management in patients with gastric retention and obstruction. A decrease in the nightly aspirate to a volume of 3 or 4 ounces suggests that the obstruction is caused by inflammation, edema and spasm, rather than by fibrous tissue, and does not require operation. Persistently large gastric aspirates, with volumes exceeding 200 or 300 ml. nightly, indicate cicatricial obstruction, necessitating surgical intervention. The electrolyte and fluid balances require careful attention in patients treated with gastric aspiration because of the loss of significant quantities of sodium, potassium and chloride.

Substances Alleged to Influence Tissue Resistance. Many substances have been alleged to improve the resistance of the upper digestive tract to ulceration. These include hormonal preparations such as pregnant mares' urine, estrogens, DOCA, parathyroid extract and various extracts of animal stomach, duodenum and colon, including robuden. There is no conclusive evidence for the therapeutic value of these materials [*18,19*].

Peptic ulcer has been attributed to a "disturbance" of the central nervous system. Recently, a new compound, chlorbenzoxamine dihydrochloride (1-[ortho-chlorbenzhydryl-2-oxethyl]-4-ortho-methylbenzylpiperazine dihydrochloride), has been proposed as an antiulcer agent, theoretically correcting this "disturbance," perhaps by improving gastric circulation [*20*]. The protective effect of this compound against experimental ulcer (pylorus ligation in rats, histamine ulcers in guinea pigs) apparently is not attributable to anticholinergic or ganglionoplegic effects since gastric secretion is unaltered. This concept lacks adequate supporting evidence, and the clinical reports available thus far are not convincing [*21,22,23*].

Other methods include the use of ten to twelve small (75 to 100 ml.) transfusions of whole blood alternating with twenty or twenty-five injections of 0.5 per cent novocaine subcutaneously or intravenously (Russia) [*24,25*], infiltration of the pneumogastric nerves with novocaine (France) [*26*], electrocoagulation of the prefrontal lobe of the brain (France) [*27*] and electronarcosis. The value of these procedures in peptic ulcer requires further study; they are not utilized in this country. Important advances in this phase of ulcer therapy will remain limited until more is learned of tissue resistance and vulnerability.

New Ulcer Cures. Countless new "cures" for peptic ulcer continue to appear, partly because prevailing methods of treatment are not entirely satisfactory, partly because of uncontrolled, overenthusiastic evaluation. The rationale for their use often is obscure, speculative or nonexistent. The list includes detergents, such as sodium alkyl sulfate, urea-formaldehyde-resins, thixotropic gels, bile salts, chlorophyll and cabbage juice. More recently advocated "antiulcer" preparations include garlic juice, chymotrypsin, oxyferriscorbone hyposulfene chloroethylamine, icthyol [*28*], dried sweet almonds, soy bean derivatives, vitamin B_1 pectin gels, glutamine [*29*], phenothiazine derivatives, silver protein-

estrogen-pectin mixtures, dl-methionine [*30*], "pituitary inhibitors," [*31*] ergotamine tartrate, "convalescent" serum from ulcer patients [*32*] and human gamma globulin; in addition, cervical and paravertebral ganglion blocks, licorice, ultrasound, prolonged sleep, diathermy and autohemolyzed blood. So-called enzyme substrate therapy is alleged to correct an "imbalance" of enzymatic activity, neutralizing intramucosal alkali in the acid-secreting cells of the stomach and intramucosal acid in the alkali-secreting cells of the duodenum. There is no conclusive evidence for this concept or for its clinical value. Compounds inhibiting the enzyme carbonic anhydrase may lower the output of hydrochloric acid after intravenous administration; however, large amounts do not demonstrably influence gastric secretion in man. Antihistaminic compounds do not decrease gastric acidity significantly and are ineffective in the treatment of peptic ulcer. The usefulness of an extract of seaweed, carrageenan, alleged to lower peptic activity in the gastric content of man, without altering pH, remains unestablished; preliminary observations in our laboratory are not encouraging. Surface-coating agents, such as emulsified dimethylpolysiloxanes, alleged to protect the ulcer from hydrochloric acid, are not useful [*33*].

Roentgen Radiation of the Stomach. Roentgen radiation to the stomach may be utilized as an adjunct in medical therapy to decrease or abolish the secretion of hydrochloric acid [*34,35*]. Approximately 1,650 r, total depth dose, are directed in ten divided treatments to the fundus and body of the stomach, via anterior and posterior portals 13 cm. square fluoroscopically outlined to conform to the fundus and the body of the stomach. There is no evidence that the radiation *per se* promotes proliferation of connective tissue or directly influences the healing of an ulcer. The inhibitory effect of radiation upon gastric secretion depends upon destruction of the parietal cells. The susceptibility of the patient to the secretory-inhibiting effects of radiation is not correlated with the degree of roentgen sickness, or with the age, sex, body weight or habitus of the individual. The antisecretory effect is variable and unpredictable. Complete achlorhydria develops in a small percentage of patients (7 per cent), continuing from several weeks to six or twelve months and in 3 per cent for periods up to five years. In approximately 40 per cent of patients, acid secretion decreases by more than 50 per cent and for long periods. The development of achlorhydria is followed invariably by complete healing of the ulcer and by no recurrence for the duration of the achlorhydria. Although the secretory inhibition is variable, the clinical course in many patients seems distinctly benefited; recurrences and complications are less frequent and the need for surgery is reduced. Among a total of 1,755 patients treated since 1937, 255 are known to be dead; fifty-two of these from cancer, including leukemia in three instances. The neoplasms included six with carcinoma of the stomach. Localized neoplastic changes in the radiated skin have been noted in two patients. The incidence of cancer of the stomach did not exceed that of the U. S. population for the year 1947, although the over-all incidence was higher due to pronounced increases primarily in cancer of the lung (right more often than left), cancer of the pancreas and cancer of the urinary bladder. A control study, still in progress, utilizing patients hospitalized during the same year but treated without radiation and matched for age and sex, thus far has revealed approximately the same incidence and distribution of deaths from cancer as in the treated group.

Gastric radiation also has been combined with the surgical procedure of antroduodenectomy. Approximately two months after operation, a depth dose of 2,000 r is delivered in divided amounts during a period of three weeks. The cobalt-60 teletherapy unit has been utilized as a source of gastric radiation; its advantages are reported to include a skin-sparing effect and greater depth dose. Roentgen radiation of the stomach has not been adopted generally despite the favorable therapeutic results. The procedure is not employed in children or young men and women. Its chief indication is for recurrent peptic ulcer not consistently controlled by careful medical management in individuals above the age of forty-five years.

Special Problems. Tobacco, Alcohol and Ulcerogenic Drugs: There is no conclusive evidence that average smoking increases gastric secretion significantly. Moderate smoking seems harmless in many instances [*36*]. Excessive smoking, on the other hand, is undesirable perhaps because of the decreased intake of food and diminished neutralization of gastric acidity. The recommendation of complete abstinence is preferable to the ineffectual suggestion of "decreasing" the quantity of tobacco. Excessive smoking reflects

increased nervous tension and the emotional disturbance is the important problem.

Since alcohol tends to increase the secretion of hydrochloric acid, its use should be avoided. Excessive drinking of coffee may irritate the gastroduodenal mucosa and reactivate peptic ulcer. Numerous medicaments may predispose to the recurrence of peptic ulcer, perhaps by irritating the gastroduodenal mucosa and increasing gastric acidity. These compounds include phenylbutazone and reserpine in large oral doses, and perhaps salicylates, corticotropin and adrenocortical steroids.

Physical and Emotional Stress: Prolonged emotional stress may increase the secretion of hydrochloric acid and the susceptibility of the gastroduodenal mucosa to injury. Consequently, rest and relief of emotional tension are important adjuncts in therapy. The needs vary with the individual. Hospitalization for several weeks is desirable in patients with persistent ulcer distress and especially with recurrent or complicated ulcers. Management of the emotional problems requires identification of the disturbing factors and intelligent efforts at their control by avoidance, "ventilation" or re-orientation of the patient, and the establishment of regular habits and a life of moderation. The support provided by the friendly yet objective physician is helpful. Formal psychotherapy usually is unnecessary. The precise role of sedatives in ulcer therapy is not clear; they do not decrease gastric secretion or motility but the relaxation and rest are beneficial. "Tranquilizing" drugs do not offer any special advantages in ulcer therapy.

PEPTIC ULCER OF THE ESOPHAGUS

Peptic ulcer of the esophagus probably is caused by the same factors involved in ulcers of the stomach and duodenum. Hiatus hernia, cardioesophageal incompetency after surgical procedures and prolonged intubation predispose to its development, by facilitating the reflux of acid-pepsin-gastric content into the esophagus. The treatment of peptic ulcer of the esophagus is essentially the same as for duodenal ulcer. Procedures such as elevation of the head of the bed during sleep, avoidance of large meals and of the recumbent position immediately after eating also are helpful to decrease acid reflux.

GASTRIC ULCER

Gastric ulcer is identical with duodenal ulcer in its clinical manifestations, course and response to antacid treatment [*37*]. The pain mechanism, acid irritation of nerve endings exposed in the ulcer crater, is the same. Hemorrhage and perforation occur in both, but unlike duodenal ulcer jejunal ulcer is uncommon after gastric resection for gastric ulcer. Most gastric ulcers are benign. They may be acute or chronic, single or multiple and large or small. Benign ulcers may occur anywhere in the stomach, including the prepyloric area and the greater curvature, but they are more common on the lesser curvature of the body of the stomach, proximal to the angulus.

Two principal attitudes prevail in the management of gastric ulcer: (1) prompt resection routinely and (2) individual evaluation and treatment, with medical management in perhaps 60 to 70 per cent of patients. Four major issues are involved: (1) the differentiation of benign and malignant gastric ulcer; (2) the theoretic hazard of malignant transformation of an originally benign ulcer; (3) the alleged increased survival of gastric cancer if all gastric ulcers were resected and (4) the advantages and disadvantages of medical and surgical treatment.

The difficulty in differentiating benign and malignant gastric ulcers seems attributable primarily to insufficient or inadequate diagnostic study. Expert and repeated examinations, together with a carefully designed and supervised therapeutic test of healing in the hospital, decrease the diagnostic error to less than 5 per cent. The error, thus, is no greater and may be less than the surgical mortality. Most of the diagnostic failures are in classifying benign ulcers as malignant and proceeding with operation, rather than in failing to recognize neoplastic ulceration. The value of the roentgen and gastroscopic methods is determined by the skill, interest, experience and facilities of the examiner, the cooperation of the patient, the index of suspicion of the clinician and the opportunity for repetition of the examination during therapy. The procedures are capable of an accuracy of at least 85 per cent. The alleged healing of neoplastic gastric ulcer has been overemphasized. Malignant ulcers rarely heal completely; suspicious radiologic findings can be demonstrated in most instances, despite significant decrease in the size of the ulcer crater. Failure of gastric ulcer to heal within two, three or four weeks does not necessarily indicate malignancy, for benign ulcers may require several months to heal completely. Exfoliative cytologic study of the gastric contents probably is the most definitive clinical

procedure for differentiating benign and malignant ulcers. The accuracy of this technic is in direct proportion to the skill and experience of the examiners; in our laboratory the reliability of the procedure approximates 95 per cent. The therapeutic test is justified when the total evidence suggests a benign ulcer and when the patient can be observed continuously and re-examined in the hospital. The objective is complete and permanent healing by x-ray and gastroscopy, supported by negative gastric cytologic study. Under such circumstances the therapeutic test may be the most decisive diagnostic method.

The unequivocal transition of an originally benign to a malignant ulcer has not been observed. Conceding the possibility on a theoretic basis, the incidence must be extremely low, less than 1 per cent. There also is no evidence of an increased frequency of gastric carcinoma in patients with benign gastric ulcer. There are no conclusive data to substantiate the view that removal of all gastric ulcers will improve the survival rate of gastric cancer. Many factors are involved, including increased surgical skill, improved methods of anesthesia, better pre- and postoperative care, chemotherapy and the more skillful use of electrolytes and fluids. Perhaps the most important factor, however, is the biologic nature of the carcinoma and the "resistance" of the individual patient to the tumor. Rapidly developing and progressive cancers terminate fatally despite prompt removal. Other cancers proceed slowly, and their resection is followed by prolonged survival, even when operation is delayed months and years.

The medical treatment of gastric ulcer, as in duodenal ulcer, is based primarily upon the effective decrease or elimination of gastric acidity. The rate of healing of benign gastric ulcer varies greatly; some ulcers heal within several weeks, others require several months. Intensive day and night therapy may be necessary in some cases. In our experience comprehensive medical treatment is successful in approximately 60 to 70 per cent of all benign gastric ulcers. In general, however, the results are not as sustained as is desirable and the limitations of medical treatment provide the principal indication for operation. Other indications for surgery in gastric ulcer are inability completely to exclude malignancy, uncontrollable or recurrent hemorrhage, ulcers associated with delayed gastric emptying (resulting from pyloric stenosis, narrowing of the antrum or contraction of the lesser curvature) and acute or chronic perforation. Ulcers on the greater curvature no longer constitute a routine indication for resection; many such lesions are benign and are to be evaluated in the same manner as ulcers elsewhere in the stomach. Relative (not absolute) contraindications to operation in gastric ulcer are extreme age, associated serious illness greatly increasing the operative risk and the ulcers associated with the ingestion of ulcerogenic drugs. Gastric resection probably should not be undertaken in poorly nourished individuals in whom the operation is likely to induce the dumping syndrome and further malnutrition.

Gastric resection is an effective operation for gastric ulcer, the favorable results ranging from 85 to 95 per cent. With highly skilled and experienced surgeons the mortality rate approximates 1 to 3 per cent; however, in less expert hands the mortality rate approximates 5 per cent and may range from 5 to 10 per cent. Despite increasing surgical skill and the concomitant therapeutic achievements, gastric resection may be a serious and at times fatal procedure. Since the postsurgical problems usually appear to be related to the magnitude of the resection, less extensive operations have been recommended, including local excision of the ulcer, with vagotomy and gastroenterostomy or pyloroplasty, hemigastrectomy and antral resection with vagotomy.

COMPLICATIONS

Approximately 10 to 15 per cent of patients with peptic ulcer require surgical treatment primarily because of complications.

Acute Perforation. Acute perforation is the most urgent indication for operation. Surgical treatment usually is limited to simple closure of the perforation. In patients with a lengthy history of ulcer recurrence, who are in excellent condition, partial gastric resection also has been recommended. Beneficial results have been reported with a program including continuous gastric aspiration, parenteral fluids, sulfonamides, antibiotics and supportive care. This program is not recommended for the usual perforation; it seems to be indicated only in patients hospitalized approximately twenty-four hours or longer after the perforation and in individuals with difficult medical problems who are hazardous operative risks.

Stenosis. Stenosis with obstruction and delayed gastric emptying is the most frequent indication for surgery in duodenal ulcer. The obstruction often is caused by inflammatory edema and spasm rather than by fibrosis, temporarily narrowing the channel through the pylorus and duodenum. It usually subsides within seven to ten days of adequate medical management, including constant gastric suction and replacement of electrolytes and fluids intravenously. Anticholinergic drugs should be avoided in the medical treatment of gastric retention secondary to active ulceration, for the inhibition of motility will further delay the emptying of the stomach. However, these compounds may be administered during continuous gastric aspiration, in an effort to lower the output of hydrochloric acid and reduce the loss of electrolytes. Operation is indicated under the following conditions: vomiting and weight loss, persistently large gastric aspirates and the roentgen demonstration of a large, dilated stomach with narrowing of the pyloric or duodenal lumen to 3 mm. or less. The surgical procedure of choice in duodenal ulcer is transabdominal vagotomy and posterior gastroenterostomy although some surgeons prefer partial gastrectomy. Ulcer of the pyloric canal, because of its strategic location, is likely to produce obstruction and gastric retention.

Massive Hemorrhage. Hemorrhage complicates the course of peptic ulcer in perhaps 20 to 25 per cent of cases. Some patients appear to have a definite tendency to recurrent bleeding. Hemorrhage is more common and more severe in postbulbar duodenal ulcer in men than in women and in patients above the age of fifty. Treatment requires meticulous care day and night and the cooperation of internist and surgeon. Therapy includes rest in bed and sedatives. If the patient is vomiting, food and drink are withheld until the vomiting subsides. Otherwise, the standard program is maintained during the day and antacid is prescribed every two hours during the night. Transfusions of whole blood are administered when the systolic blood pressure falls to below 100 mm. Hg, when the pulse rate much exceeds 100, when the erythrocyte count decreases to below 3 million per cubic millimeter or when there is continued severe hemorrhage regardless of any criteria. Antisecretory drugs may be prescribed, provided there is no delay in gastric emptying and bowel function is regulated with laxatives. In patients with severe bleeding from known duodenal ulcer, continuous gastric aspiration may be beneficial; very occasionally the intragastric drip may be employed. The program is maintained until the erythrocyte count and the hematocrit are stabilized and the feces are negative for occult blood. The subsequent treatment is that outlined for uncomplicated peptic ulcer. The hemorrhage induced by ulcerogenic drugs usually responds to medical management, including discontinuance of the medication.

Gastric hypothermia recently has been utilized successfully in the control of massive hemorrhage from peptic ulcer [*38*]. The intragastric perfusion of a cooling solution of ethyl alcohol and ice water with a temperature of 1° to 5°C. lowers the temperature of the gastric mucosa to between 10° and 14°C. The beneficial effect is attributable to a direct inhibitory effect upon the parietal and chief cells, decreasing the secretion of acid and pepsin and diminishing the digestive property of the acid gastric juice. The inhibitory effect disappears promptly after cessation of the perfusion.

Surgery is indicated in bleeding peptic ulcer under the following conditions: (1) severe, persistent hemorrhage during medical treatment, especially in patients above the age of fifty, (2) recurrent bleeding, (3) stomal ulcer with hemorrhage, (4) hemorrhage and perforation and (5) hemorrhage and pyloric obstruction. The decision for operation usually is made during the first forty-eight to seventy-two hours because complications and mortality rise with persistent uncontrolled hemorrhage. The operation of choice in massive hemorrhage from peptic ulcer is partial gastric resection, excision of the lesion, if possible, and ligation of the bleeding vessel. Surgery does not completely protect against recurrent hemorrhage although the possibility is greatly reduced.

Jejunal Ulcer. Jejunal ulcer presents a difficult therapeutic problem because of the tendency of the lesion to penetrate, bleed or perforate. Some patients respond to careful medical management in the hospital, including gastric radiation. Usually, however, surgery is preferred, namely, transabdominal vagotomy with or without further gastric resection depending upon the circumstances. The association of pronounced gastric hypersecretion and recurrent jejunal ulceration should suggest the possibility of an "endocrine ulcerogenic" mechanism involving a non-insulin secreting islet-cell tumor

of the pancreas or an adrenocortical or parathyroid adenoma.

Gastrojejunocolic fistula is treated initially by restoration of nutrition with a diet high in proteins, calories and supplements, and the correction of electrolyte and fluid imbalance. The operative procedure consists in resection of the fistula, reconstruction by means of gastroenterostomy and a more adequate gastric resection or vagotomy.

Intractability. The classification, "intractability," in peptic ulcer frequently is misused as a substitute for poor medical management. Many apparently refractory ulcers are the result of poor cooperation of the patient or inadequate treatment prescribed by the physician. Correction of these reversible situations facilitates healing of the ulcer without operation. Intractability is more common in men than in women and in pyloric channel, postbulbar and gastric ulcers. Gastric hypersecretion may be so intense as to resist all antacid and antisecretory measures as in ulcers associated with certain endocrine abnormalities. So-called intractable ulcer pain is not always a valid basis for operation. Very often persistent pain reflects ineffective therapy and the pain disappears completely when gastric acidity is controlled adequately.

Other Complications. Medical treatment itself may induce troublesome complications, including fecal impactions and stercoral ulceration during the unregulated use of constipating antacids (calcium carbonate and aluminum hydroxide). Electrolyte disturbances comprise chiefly the hypernatremic alkalosis sometimes noted after excessive ingestion of sodium bicarbonate and the hypercalcemic syndrome produced occasionally by very large intakes of milk, baking soda and/or calcium carbonate. The excessively restrictive diets of earlier years occasionally maintained and increased existing nutritional deficiencies, but such defects in peptic ulcer now are rare. Anticholinergic drugs may cause atony of the bladder and urinary retention in elderly men with prostatic hypertrophy, and temporary intestinal atony in nutritionally depleted patients.

Surgical treatment may cause serious complications, at times more difficult to manage than the original ulcer. These problems include disturbed gastrointestinal motility and recurrent ulcer after vagotomy and gastroenterostomy, the dumping syndrome, nutritional disturbances, obstruction of the afferent loop, in addition to stomal ulcer and gastrojejunocolic fistula.

Prevention of Recurrences. The immediate results of effective therapy in peptic ulcer are good, with prompt relief of pain and complete healing. The long term results are less encouraging. Recurrences of peptic ulcer are frequent with almost any type of therapy, medical or surgical, which does not abolish acid secretion permanently. The precipitating factors recognized and emphasized most often are physical fatigue, emotional stress, dietary indiscretions, including excessive alcohol and coffee, irritating drugs and intercurrent illness. There are no specific measures that completely protect against recurrences, except the production of achlorhydria. However, the tendency to recurrences may be lessened and their severity decreased by a comprehensive program, including (1) thorough treatment of the initial lesion and careful supervision of the patient subsequently, (2) education of the patient as to the nature of the disease and the objectives of treatment, (3) a practical but efficient program of acid control, (4) avoidance of alcohol, tobacco and irritating drugs and foods, (5) sufficient rest and sleep, (6) resolution of emotional problems, if possible, and (7) proper care of respiratory infections and other intercurrent illness.

CONCLUDING REMARKS

Despite the limitations of medical management, current methods of treatment, when applied properly, are effective in most patients with uncomplicated peptic ulcer. The ultimate results depend upon many factors: the location and size of the ulcer; the presence or absence of complications; the emotional status, intelligence and cooperation of the patient; the physician's knowledge, continued interest and resourcefulness; and the prolonged maintenance of a reasonable program. Casualness and carelessness are important causes of failure of therapy. Treatment should not be confined to a single measure. The emphasis should be on total management, including antacids, antisecretory drugs and sedatives, avoidance of gastrointestinal irritants and skillful attention to emotional problems. The continued investigation of hormonal influences and intracellular enzyme systems possibly involved in tissue resistance and in the secretion of hydrochloric acid, of secretory inhibitors in the gastric content, gastroduodenal blood flow and of genetic factors, ultimately may reveal medical technics for the control of gastric secretion and for enhancing tissue resistance to peptic ulcer. One of the important needs in the further

investigation of the ulcer problem is carefully controlled study of its course and of the possible influence of various therapeutic measures.*

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Clinical Studies

Fatal Complications of Virus Hepatitis in Two Patients with Agammaglobulinemia*

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IN RECENT years the concept of autoimmune disease has become extremely popular. The occurrence of marked hypergammaglobulinemia, prominent plasmacytosis in the inflammatory exudate, positive lupus erythematosus phenomena and complement-fixing antibodies against liver in some cases of hepatic disease [*1–4*] has given rise to the concept that chronic hepatitis and postnecrotic cirrhosis following attacks of virus hepatitis might represent autoimmune disease of the liver. In fact, it has even been postulated that hepatic damage occurring during the course of acute virus hepatitis might be the result of hypersensitivity to the virus [*5*].

There is, of course, an alternative and equally attractive, perhaps more direct hypothesis; namely, that the liver damage in chronic hepatitis and postnecrotic cirrhosis following virus hepatitis may be due to persistence of the virus infection in the tissue. This hypothesis would regard the plasmacytosis and hypergammaglobulinemia as results of prolonged antigenic stimulation by the virus.

It is the purpose of this report to describe the occurrence of severe cirrhosis and subacute yellow atrophy of the liver in two patients with agammaglobulinemia. In both of these patients, one with acquired agammaglobulinemia and one with the congenital, sex-linked form of the disease, the gamma globulin levels were extremely low and the immunologic responsiveness almost completely absent. The occurrence of these forms of liver disease in these patients is strong evidence that the pathogenesis of neither acute yellow atrophy nor chronic hepatitis with postnecrotic cirrhosis depends upon plasma cells, gamma globulin or production of large amounts of circulating antibody. These observations, together with those in the case observed by Janeway and Gitlin [*6*], indicate that patients with agammaglobulinemia may be extremely susceptible to the destructive effects of virus hepatitis.

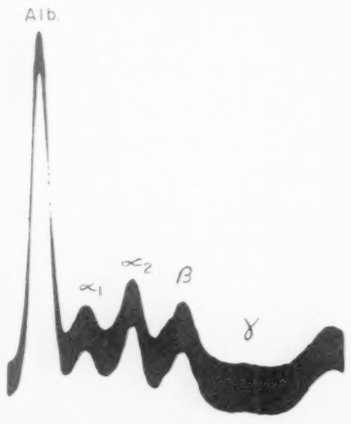


FIG. 1. Case 1. Free electrophoretic pattern of the serum from a fifty-four year old man with acquired agammaglobulinemia, showing absence of gamma globulin.

CASE 1. A white, male farmer, fifty-four years of age, had a productive cough, night sweats, anorexia and exertional dyspnea. Sputum studies for tuberculosis were negative. Roentgenograms of the chest revealed an anterior mediastinal mass. Ten months after the onset of symptoms a thoracotomy was performed and a solid, well circumscribed tumor was removed. On histologic examination this proved to be a benign thymoma. The patient felt well for six months following the operation and was asymptomatic. Then he had pneumonia which responded to antibiotic therapy. During the next twenty-two months he had twelve attacks of pneumonia.

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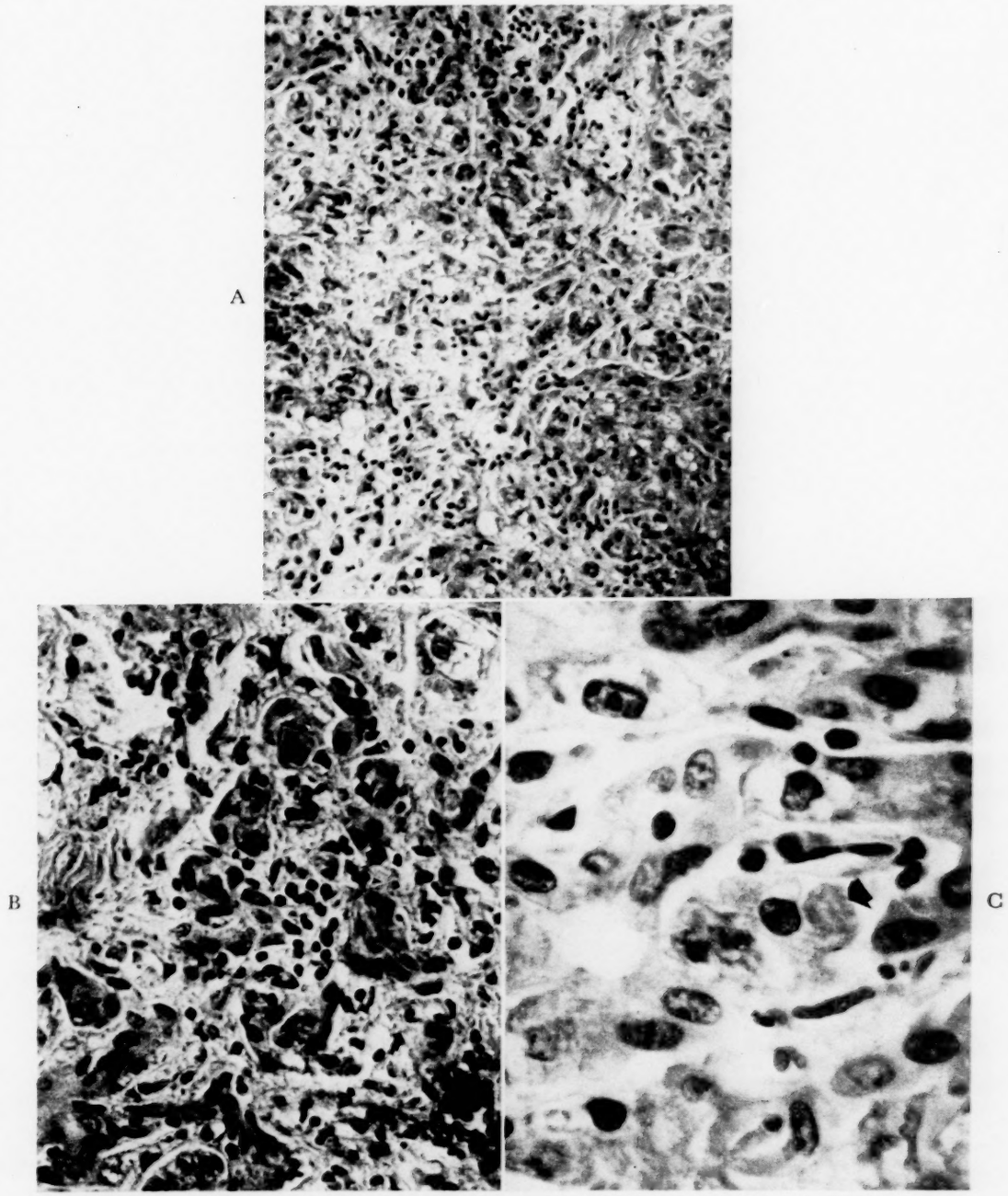


FIG. 2. Case 1. Photomicrographs of the liver obtained at autopsy. A, low power view demonstrating the massive central lobular necrosis. Original magnification × 100. B, medium power view of a portal area showing infiltrate of lymphocytes and neutrophils. Original magnification × 250. C, high power view of damaged liver cell demonstrating an eosinophilic cytoplasmic inclusion body. Original magnification × 600.

A diagnosis of agammaglobulinemia was established by electrophoretic study of the patient's serum two and a half years following surgery. Further studies revealed that the patient was unable to form antibodies to a wide variety of bacterial and viral antigens after intensive antigenic stimulation. The gamma globulin concentration ranged between 40 and 80 mg. per cent as measured by an immunochemical technic, and the isoagglutinin titer revealed no isoagglutinins or very low titer on several determinations. Figure 1 demonstrates the free electrophoretic pattern of this patient's serum.

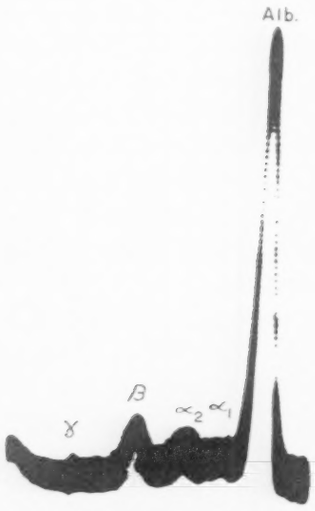


FIG. 3. Case II. Free electrophoretic pattern of the serum prior to the start of prophylactic gamma globulin therapy, showing the absence of gamma globulin.

In addition to the pulmonary difficulties the patient had a history of arthritis of the wrists, elbows, knees and shoulders.

Eight months after the diagnosis of agammaglobulinemia and prior to the administration of any gamma globulin for the prophylaxis of infection, anorexia and mild epigastric distress developed, followed in two weeks by the insidious onset of jaundice. The patient's arthritis completely disappeared after the onset of jaundice. Physical examination at this time revealed marked icterus and a palpable, non-tender liver. Laboratory studies revealed bilirubinuria and hyperbilirubinemia. The serum bilirubin was 6.8 mg. per cent direct and 10.9 mg. per cent total. Thymol turbidity was 1 unit and the cephalin-cholesterol flocculation test gave a trace reaction. The prothrombin time was 23.8 seconds, with a control of 13.1 seconds.

A tentative diagnosis of serum hepatitis was made, and extensive gamma globulin was administered in the hope that this would help control the disease. The patient was given 100 cc. of gamma globulin immediately, and this dosage was repeated one week later. In addition, a course of oral vitamin K and oral neomycin to sterilize the gut was started.

The course of the disease was rapidly progressive; one week after the onset of the jaundice the patient was in impending coma and an amine odor could be detected on his breath. Laboratory studies now revealed serum bilirubin 13.2 mg. per cent direct and 21.1 mg. per cent total; thymol turbidity 19 units; cephalin flocculation test trace; and prothrombin time 39.5 seconds, with a control of 13.8 seconds. Treatment with ACTH, 50 mg. given intravenously daily, was initiated and he was also given vitamin K intravenously. His condition continued to deteriorate and he died three days later in hepatic coma.

At autopsy the gastrointestinal tract was filled with blood. There were hemorrhage and necrosis around the pancreas, and the transverse colon and the lesser omental sac were filled with clotted blood. The liver weighed 1,300 gm., was flabby, and on cut section was pale yellow. The kidneys showed many cortical hemorrhages. Microscopic examination of the liver revealed massive centrolobular necrosis and periportal infiltration of neutrophils and lymphocytes. (Figs. 2A and B.) Some of the damaged liver cells contained eosinophilic cytoplasm inclusion bodies. (Fig. 2C.) There was evidence of acute pancreatitis with infiltration of neutrophils and degeneration of the acinar cells in the pancreas.

This case is clinically and pathologically consistent with acute viral hepatis progressing to subacute yellow atrophy or massive necrosis of the liver. The pancreatitis probably contributed to the patient's rapid death, but the pathologic changes in the liver were undoubtedly sufficient to cause death.

CASE II. A white male child was observed closely from birth, with frequent determinations of gamma globulin being made because his older brother was known to have agammaglobulinemia. Gamma globulin failed to develop in this patient and the diagnosis of congenital agammaglobulinemia was firmly established by the time the child was six months old. Figure 3 shows the free electrophoretic pattern of his serum. The patient was started on a regimen of gamma globulin therapy at the age of nineteen months. He was given 20 cc. of gamma globulin monthly until the age of three and a half years when the dose was increased to 40 cc. monthly. During the six months prior to his admission to the hospital intramuscular injections of gamma globulin were the only injections he received.

At the age of four years the patient was admitted to the hospital because of jaundice which developed after five days of anorexia and vomiting. On physical examination a firm, non-tender liver was palpable 6 cm. below the right costal margin. The spleen was not palpable. Laboratory studies revealed bilirubin 4.7 mg. per cent direct and 8.5 mg. per cent total; bromsulfalein retention 25 per cent in forty-five minutes; thymol turbidity 2 units; cephalin flocculation test negative; and prothrombin time 18.3 seconds, with a control of 13.4 seconds.

A tentative diagnosis of serum hepatitis was made, and the patient was given 120 cc. of gamma globulin oral neomycin and vitamin K. The patient's liver function tests and clinical condition improved gradually during the next five weeks. On discharge from the hospital the patient felt well although physical examination still revealed scleral icterus, and the liver was still enlarged. The serum bilirubin was 1.3 mg. per cent direct and 2.8 mg. per cent total.

Five weeks after discharge from the hospital the

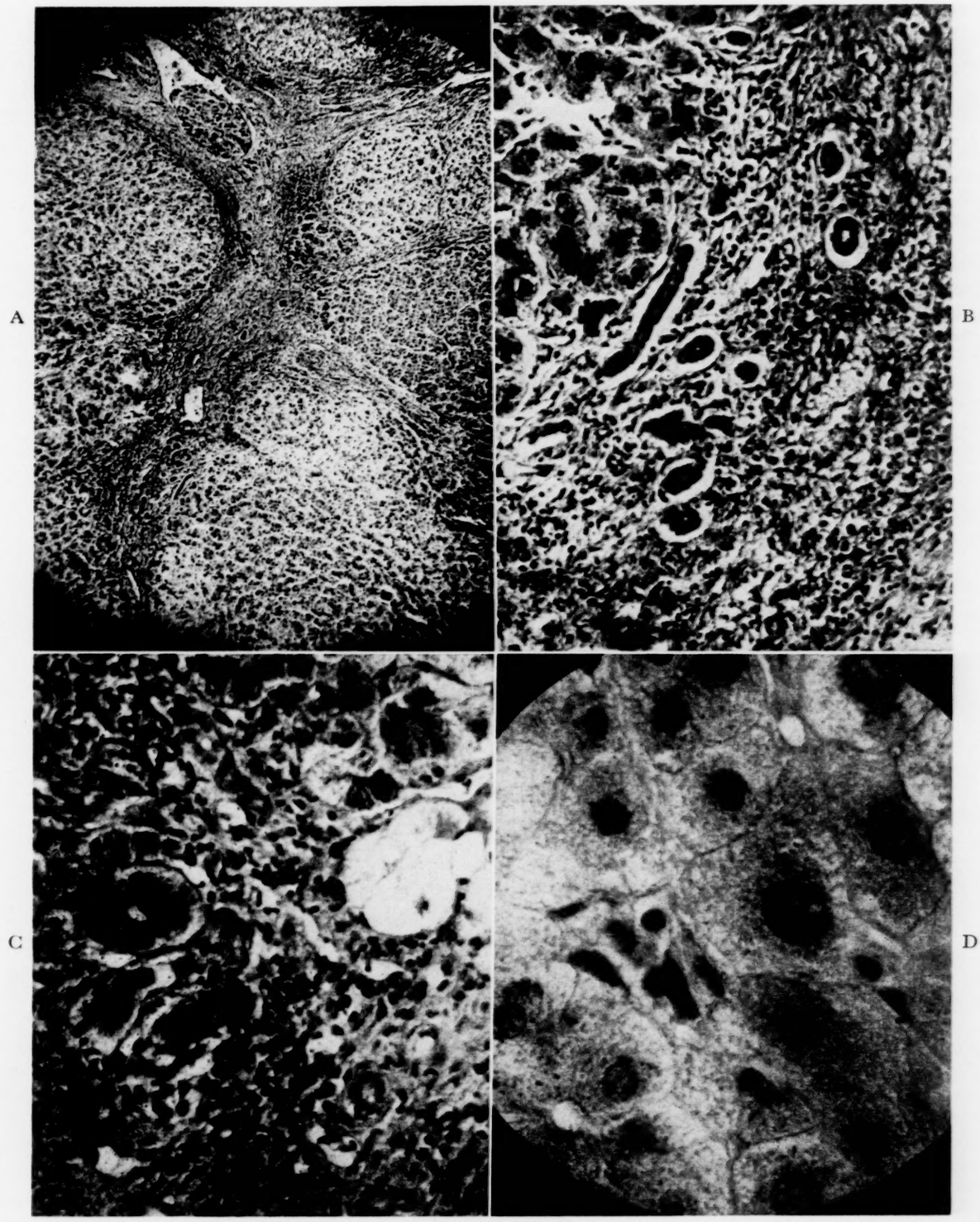


FIG. 4. Case II. Photomicrographs of a liver biopsy specimen obtained two weeks prior to death. A, low power view showing fibrosis and nodular regeneration. Original magnification × 40. B, medium power view revealing bile duct regeneration and periportal round cell infiltration. Original magnification × 150. C, high power view showing degenerating parenchymal cells and round cell infiltration. Original magnification × 400. D, high power view demonstrating intranuclear inclusion bodies. Original magnification × 800.

patient was readmitted because of recurrence of more severe jaundice and anorexia. Physical examination revealed jaundice, a distended abdomen with a palpable fluid wave, and the liver palpable 5 cm. below the right costal margin. Laboratory studies revealed serum bilirubin 3.6 mg. per cent direct and 7.5 mg. per cent total; thymol turbidity 1 unit; reaction to the cephalin flocculation test trace; and prothrombin time 22.8 seconds, with a control of 13.6 seconds. At this time the serum glutamic-oxalacetic transaminase level was 2,220 units.

Because the patient's condition was rapidly deteriorating, steroid therapy was decided upon. He was given 180 mg. (300 mg./M^2/twenty-four hours) of cortisone daily, 50 mg. neomycin three times a day, 5 mg. vitamin K twice a day and 30 cc. gamma globulin weekly. Cortisone therapy was discontinued because of hypertension after twenty-four days, and therapy with triamcinolone, 24 mg. daily, was started. The patient's condition continued to deteriorate, with increasing abdominal distention, increasing jaundice and prolonged prothrombin time for two weeks. During the following six weeks there was a gradual improvement in both clinical condition and laboratory test results. During this time his bilirubin decreased to 0.7 mg. per cent direct and 1.6 mg. per cent total. The prothrombin time improved from a high of 60 seconds to 17.6 seconds. The serum glutamic-oxalacetic transaminase fell from 2,220 units to 82 units. Although the patient felt well, he continued to have hepatomegaly and ascites. He was discharged from the hospital on a regimen of gradually decreasing doses of triamcinolone as well as continued vitamin K and 30 cc. gamma globulin weekly.

The patient's condition remained about the same for five months, but two months after the withdrawal of steroids his condition deteriorated again with increasing jaundice and malaise. Physical examination revealed the liver to be palpable 6 cm. below the right costal margin and the abdomen to be distended with fluid. The abdominal veins were markedly distended. Laboratory values revealed bilirubin 3.9 mg. per cent direct and 6.8 mg. per cent total; thymol turbidity 1 unit; cephalin flocculation test 1 plus; bromsulfalein retention 23 per cent in forty-five minutes; and serum glutamic-oxalacetic transaminase 1,455 units.

An open liver biopsy was performed. On gross examination the liver was described as nodular, enlarged and fibrotic. Microscopic examination revealed distortion of the normal lobular pattern by fibrosis. There were many areas of nodular regeneration of parenchymal cells. There was a marked infiltration of periportal round cells and adjacent parenchymal cells showed degenerative changes. There was new bile duct formation in the portal spaces. Intranuclear inclusion bodies were frequently noted, but no cytoplasmic inclusion bodies were present. It was of interest that the inflammatory cell infiltrate was completely lacking in plasma cells. (Fig. 4.) This is the only instance in which we have ever discovered the pathologic picture of postnecrotic cirrhosis in the absence of plasma cells.

Cortisone therapy (250 mg./M^2/day) was resumed. The patient's condition rapidly deteriorated and he died in hepatic coma two weeks later. Autopsy revealed the same pathologic condition noted in the biopsy specimen of the liver: ascites and an enlarged, finely nodular liver, with the histology previously described.

This case probably represents serum hepatitis progressing to postnecrotic cirrhosis in a child with congenital agammaglobulinemia.

COMMENTS

We think that both of these cases stemmed from infection with hepatic virus B for the following reasons: (1) There was no history of exposure to infectious hepatitis or any hepatotoxins. (2) One patient (Case II) was receiving monthly injections of gamma globulin which should have provided adequate protection against infectious hepatitis. (3) The first patient (Case I) was subjected to extensive studies requiring frequent needle punctures which could provide portal of entry of homologous hepatitis virus. In the second patient (Case II), the needle punctures required by the monthly injections of gamma globulin could provide the means of entry of this agent.

Apparently patients with agammaglobulinemia are unable to combat the hepatitis virus adequately. This is surprising because there is abundant evidence that these patients are able to cope with many other virus diseases in a satisfactory manner. For example, in our experience these patients have had measles, mumps, German measles, chickenpox, vaccinia, APC virus infections and poliomyelitis with normal clinical courses. In addition, and more strikingly, some of them have been repeatedly exposed to classic cases of measles and chickenpox both in the home and intimately on the hospital ward. Furthermore, an accelerated and immune reaction to vaccinia virus has developed without the demonstration of significant antibodies. This capacity to resist virus infections may be a function of non-specific mechanisms of resistance to infection, specific immunity dependent upon cellular adaptation independent of production of gamma globulin and circulating antibody, and/or small amounts of specific circulating antibody below the threshold of even the most delicate methods of measurement used. What-

ever the explanation may be, there can be no question of the capacity of these patients to resist certain virus infections.

That this capacity cannot be generalized to include all virus infections is suggested by the observations included in this report. In the only two patients in our series of twenty-seven patients with agammaglobulinemia in whom hepatitis developed, infection of the liver resulted in death. Similarly, the single patient in Janeway's series in whom hepatitis developed died after a prolonged illness. In Case I, we have noted the course which might be expected from a virus infection in a patient lacking defense mechanisms against the virus, namely, an overwhelming, destructive disease with a rapidly progressive course. There is little support in this case for the belief that acute or subacute atrophy of the liver, occasionally stemming from infection with hepatitis viruses A or B, is a hypersensitivity reaction depending upon antibody production.

Case II presents an entirely different picture of the clinical course, featured by exacerbations and remissions with general, progressive, destructive change. This suggests that defense mechanisms are operative but not sufficiently effective.

In the past we have been attracted, as have other investigators, to the hypothesis that autoimmune mechanisms play some role in the development of chronic hepatitis and the occurrence of postnecrotic cirrhosis of the liver. After studying this patient (Case II) the attraction of this hypothesis is much weaker. The evidence which seemed to favor such a belief in the immunologically intact person, namely, the hypergammaglobulinemia, the plasmacytosis of the diseased liver and the presence of circulating, complement-fixing antibody, was sought in this patient (Case II), but not found. Even the characteristic waxing and waning of the disease and the response to steroid therapy, which have been interpreted as evidence for the operation of the immune response, were present in this patient with agammaglobulinemia. Furthermore, the histologic changes of the liver in this patient showed the typical changes of postnecrotic cirrhosis, with one exception, namely, the complete absence of plasma cells.

Thus postnecrotic cirrhosis of the liver could develop in this patient with agammaglobulinemia without evidence of a capacity to form circulating antibody or to produce and release gamma globulin. It must be remembered, however, that the possibility still exists that even though subacute atrophy of the liver and/or postnecrotic cirrhosis can occur in patients with extreme hypogammaglobulinemia or agammaglobulinemia, they may have an immunologic basis. This statement rests upon the possibility that minute amounts of antibody below the threshold of detection might be produced by these patients and could be responsible for the pathologic changes observed, and the known fact that in patients with even the most severe agammaglobulinemia, the capacity for development of delayed allergy exists [*7–9*]. However, we interpret these observations as strong support for the hypothesis that the plasmacytosis of liver and bone marrow and the hypergammaglobulinemia, usually observed in patients with postnecrotic cirrhosis and chronic hepatic disease, are secondary phenomena (perhaps a function of the prolonged presence of a virus which cannot be eliminated) rather than important pathogenetic indications. We believe the overwhelming destruction of hepatic parenchyma in acute and subacute atrophy of the liver following virus hepatitis and the occurrence of postnecrotic cirrhosis following virus hepatitis may be more directly attributable to the action of the virus itself, together with the host's nonspecific response mechanisms.

The observation of the occurrence of diseases considered by some investigators to be due to the formation of autoantibodies, in patients with agammaglobulinemia should place doubt on the conclusion that an unknown pathogenic mechanism plus hypergammaglobulinemia plus plasmacytic response plus tissue or organ-specific circulating antibodies add up to a specific immunologic pathogenesis.

SUMMARY

Two patients with agammaglobulinemia who died of complications of a disease presumed to be homologous serum hepatitis are described. The occurrence of acute atrophy in one patient and typical postnecrotic cirrhosis in the other has induced critical evaluation of the concept that an autoimmune mechanism is important in the pathogenesis of either of these complications of virus hepatitis.

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Hereditary Non-Spherocytic Hemolytic Disease*

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HEREDITARY hyperbilirubinemia with an indirect van den Bergh reaction is most frequently attributable to a well delineated hemolytic state. Once the hemoglobinopathies, thalassemia, hereditary spherocytosis and elliptocytosis are excluded we are left with three relatively uncommon disorders: hereditary non-spherocytic hemolytic disease, constitutional hepatic dysfunction and the Crigler-Najjar syndrome.

Hereditary non-spherocytic hemolytic disease is an intracorpuscular hemolytic disorder in which the specific red cell abnormality has remained obscure. There is no consistent morphologic appearance of the red cell as in the other intrinsic erythrocytic disorders. The disease is familial, probably being transmitted as a Mendelian dominant gene. The recognition of hereditary non-spherocytic hemolytic disease is clinically important since splenectomy is of no value [*1–20*].

The second group comprises patients with constitutional hepatic dysfunction (Gilbert's disease). This disorder also is familial in origin and is thought to be transmitted as a dominant character with incomplete manifestations. It is characterized by the presence of relatively mild indirect hyperbilirubinemia with absence of other findings of hemolytic or hepatic disease [*21–30*].

The third disease in this group is the Crigler-Najjar syndrome, which differs from constitutional hepatic dysfunction in that the non-hemolytic jaundice is more severe and may be associated with kernicterus. The disease is usually diagnosed in childhood. Recently, a defect in glucuronide conjugation has been demonstrated as the possible basis of this disorder [*31–33*].

Although not a hereditary disorder, the indirect bilirubinemia occurring in patients who have recently had hepatitis is often extremely difficult to differentiate from the first two disorders [*34–37*]. An elevated indirect van den Bergh reaction may persist for years following hepatitis without other chemical or morphologic evidence of hepatic disease. When it is impossible to document an episode of acute hepatitis or demonstrate a familial incidence of jaundice, this posthepatitic state is clinically inseparable from constitutional hepatic dysfunction. Occasionally, these patients exhibit a mild acquired (extracorpuscular) hemolytic state [*35*]. This may be differentiated from hereditary non-spherocytic hemolytic disease by red cell survival studies.

The chronic idiopathic jaundice described by Dubin and Johnson [*38*] and the cases of non-hemolytic jaundice described by Rotor et al. [*39*] resemble these conditions because of the frequent history of prolonged jaundice and familial incidence. The Dubin-Johnson syndrome can be diagnosed by demonstration of the characteristic pigment in the liver and in both conditions there is an elevation in the "direct" reacting serum bilirubin.

During the past four years we have studied twenty-one patients with mild indirect bilirubinemia and without morphologic abnormalities of the erythrocytes. The group includes all such patients admitted to Walter Reed Army Hospital since January 1955. Essentially, the problem was one of differential diagnosis between hereditary non-spherocytic hemolytic disease and constitutional hepatic dysfunction. The purpose of this paper is to enumerate the similarities and differences, and to demonstrate the means whereby the differential diagnosis can be made. Most significant has been the relative incidence of the diseases; of the twenty-

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one patients studied, twenty had hereditary non-spherocytic hemolytic disease and only one was diagnosed as having constitutional hepatic dysfunction.

METHODS

Red cell survival studies were performed by tagging the patient's blood or freshly donated compatible blood with radioactive Cr^{51} [*40*]. Thereafter, serial specimens were collected three times weekly until it was determined that 50 per cent of the transfused cells had disappeared from the blood. The best-fit curve was plotted on semilogarithmic paper. The range of normal values for the T/2 of Cr^{51} on transfused red cells in this laboratory is twenty-seven to thirty-five days.

Red cell counts were performed by the method of Dacie [*41*]. Hemoglobin concentration was determined by the cyanmethemoglobin method [*42*]. The packed cell volume was measured by the microhematocrit technic [*43*]. Reticulocyte counts were performed utilizing Brecher's method [*44*]. Hemoglobin type was established by paper electrophoresis [*45*]. Fetal hemoglobin was measured as an alkali-resistant component [*46*]. The Coombs' test, acid serum and heat fragility tests were performed as described by Dacie [*41*]. Plasma hemoglobins were determined by a quantitative method [*47*]. Osmotic fragility tests were carried out by the method of Dacie [*41*]. They were also performed on sterile defibrinated blood after incubation for twenty-four hours at 37°C. [*41*]. *In vitro* tests for Heinz body formation were made by the method of Beutler [*48*]. Serum iron was determined by the method of Ramsay [*49*] and the unsaturated iron-binding capacity of the serum by the method of Ventura [*50*]. The tests of hepatic function included bromsulfalein excretion (using 5 mg. per kg. dosage and determining the degree of dye retention after forty-five minutes) [*51*], cephalin flocculation by a modification of the method of Hanger [*52*], thymol turbidity by a modification of the procedure of Maclagen [*53*], alkaline phosphatase by the Shinowara-Jones-Reinhart modification of the Bodansky method [*54*] and the serum bilirubin by the method of Malloy and Evelyn [*51*]. Serum proteins and the albumin and globulin fractions were determined by the Weichselbaum modification of the Kingsley biuret method [*55*] and by paper electrophoresis [*56*].

CRITERIA FOR DIAGNOSIS

The diagnosis of hereditary non-spherocytic hemolytic disease can be made in many patients by establishing the existence of a familial incidence of the disorder and demonstrating increased destruction of red cell (anemia, elevated "indirect" bilirubin and increased fecal urobilinogen) or signs of accelerated production of red cells (reticulocytosis and erythroid hyperplasia). However, when the hemolytic disorder is mild, any or all of these parameters of hemolytic disease may be absent [*57,58*] and one of the methods of measuring erythrocyte life span must be employed. Either isotope-tagged red cells or biologically labeled erythrocytes (Ashby technic) may be utilized to study red cell survival [*40,59*].

Once accelerated destruction of red cells has been established, it is essential to demonstrate that the erythrocytic defect is intracorpuscular before the diagnosis of hereditary non-spherocytic hemolytic disease can be established. A negative reaction to the Coombs' test and demonstration of hemolytic disease in other members of the family provide presumptive evidence of an intrinsic hereditary red cell abnormality. The Coombs' test, however, is not positive in all cases of acquired hemolytic anemia. Thus, when a familial incidence of hemolysis cannot be established differential red cell survival studies are necessary to demonstrate whether the defect is intracorpuscular (hereditary) or extracorpuscular (acquired). Normal cells transfused into patients with an extracorpuscular hemolytic anemia are rapidly destroyed while normal cells survive at the usual rate in patients with hereditary non-spherocytic hemolytic disease.

Hereditary non-spherocytic hemolytic disease is, finally, a diagnosis of exclusion. It can be made only when the other more clearly defined intracorpuscular hemolytic disorders cannot be demonstrated. The hemoglobinopathies can be readily excluded by the demonstration of normal adult hemoglobin. Thalassemia is characterized by the presence of a microcytic hypochromic anemia. There are usually increased amounts of fetal hemoglobin and A_2 hemoglobin. Paroxysmal nocturnal hemoglobinuria is differentiated by the acid and heat fragility tests, the thrombin test and the presence or absence of hemoglobinemia [*41*]. The absence of a megaloblastic bone marrow usually suffices to exclude pernicious anemia. Hereditary elliptocytosis and hereditary spherocytosis are identified by the characteristic morphology of the red cells.

In most cases there is little difficulty in separating hereditary non-spherocytic hemolytic disease from the other disorders with intrinsic red cell abnormalities. Examination of the peripheral smear and the performance of relatively simple laboratory procedures usually

provides a clear cut differential. When hemolysis is mild the great difficulty is to differentiate hereditary non-spherocytic hemolytic disease from the non-hemolytic states with mild jaundice. Constitutional hepatic dysfunction and the posthepatitic state with an elevated indirect van den Bergh reaction may be clinically inseparable from hereditary non-spherocytic hemolytic disease. The demonstration of an intracorpuscular hemolytic defect by red cell survival studies is frequently the only method of establishing the diagnosis.

PATIENTS

Our series of patients included only one child, nine years of age, and one adult over forty years of age. There were three young adult female patients. (Table 1.)

Jaundice was first observed in childhood in six of our patients (Cases 1, 3, 4, 5, 6 and 9). In two patients in this group it was noted initially in the first year of life. Eighteen patients had been aware of jaundice for periods varying from six months to twenty years. These patients were transferred to this installation with the diagnosis of either "hemolytic anemia" or "chronic hepatic disease." The latter diagnosis was made more frequently, but review of medical records revealed no evidence to support a diagnosis of hepatitis. One patient (Case 15) was not icteric and had no history of jaundice. A hemolytic disorder was noted during family studies which were undertaken because of the jaundice and anemia of her son (Case 4). Another patient (Case 11) was admitted to this hospital with cardiovascular disease and icterus was incidently noted.

Ten patients in whom a definitive etiology had not been established had a family history of jaundice. The mother and sister of one patient (Case 9) had undergone surgery for gallstones. Increased reticulocyte counts without definitive morphologic abnormalities of red cells were demonstrated in the close relatives of six of our patients (Cases 2, 3, 4, 6, 12 and 15).

The patients complained most frequently of weakness and fatigue. Headaches were common. Gastrointestinal complaints of fullness, eructation, vague distress in the right and left upper quadrant, nausea, constipation and diarrhea were frequent, often varying considerably in intensity from one day to the next. Intermittent episodes of weight loss were reported by several patients. The symptoms were unrelated to exertion or diet. In several instances they seemed to occur following infections of the upper respiratory tract.

Physical examination revealed scleral icterus when the plasma bilirubin was in excess of 1.5 to 2 mg. per 100 ml. The spleen was palpably enlarged in seven patients. In four additional patients it had been palpable prior to splenectomy. The spleen was not clinically enlarged in nine patients. The liver edge was palpable in ten patients. It was normal in consistency with a firm edge. In no patient was the liver thought to be clinically enlarged.

Blood smears were examined in all patients. Mild anisocytosis and poikilocytosis were demonstrable in most of the smears. Target cells and Howell-Jolly bodies were seen in the blood smears of patients who had undergone splenectomy. Basophilic stippling of the red cells was not noted. No spherocytes or elliptocytes were seen in the smears, and the rouleaux which formed in fresh blood under coverslips appeared normal [*2,60*]. Two patients (Cases 4 and 12) had increased Heinz-body formation as demonstrated after incubation of the patients' blood in a solution of acetyl phenylhydrazine. This study was not performed in the other patients. Anemia (hemoglobin less than 12 gm. per cent) was present in five patients, and occurred in only those with evidence of brisk red cell destruction. The mean corpuscular volume was slightly increased in this same group of patients and was thought to be due to reticulocytosis. Reticulocytes in excess of 2 per cent were present in fifteen of the patients with hereditary non-spherocytic hemolytic disease. They were more numerous in patients with shorter red cell life spans. Results of studies on osmotic fragility were within normal limits in all patients. In four patients there was a slight increase in the osmotic fragility of the cells after twenty-four hours' incubation (Cases 3, 5, 7 and 11). The plasma hemoglobin was within normal limits (less than 5 mg. per 100 ml.) in ten patients in whom it was tested. The reaction to the Coombs' test was negative in all patients. The electrophoretic mobility of hemoglobin was that of normal adult hemoglobin (hemoglobin A) in all patients. The fetal hemoglobin in each case was less than 2.5 per cent. Results of the acid hemolysis and heat fragility tests for paroxysmal nocturnal hemoglobinuria were negative.

Nineteen patients had hyperbilirubinemia with an increase only in the indirect van den

TABLE

SUMMARY OF DATA FROM TWENTY-ONE PATIENTS WITH HEREDITARY HYPER

Case No.	Age (yr.) and Sex	Race	Age at Onset of Disease (yr.)	Family History of Jaundice or Cholelithiasis	Jaundice†	Liver‡	Spleen‡	Red Cell Life Span T/2 Cr^{51} (days)		Serum Bilirubin (mg./100 ml.)		Reticulocytes (%)	Hemoglobin (gm./100 ml.)
								Auto-transfused	Donor Cells	Total	Direct		
1	20, F	C	8	Mother	I	0	+	7	...	1.7	0.7	20	9.0
2	22, M	C	20	Brother	I	+	+	7	...	3.5	0.5	9.5	12.7
3	20, M	C	9 mo.	Brother	I	+	+	7	26	3.5	0.5	7.4	11.9
4	9, M	C	3 mo.	Mother (Case 15)	P	+	+	9	...	4.8	0.0	5.0	10.4
5	20, F	C	Childhood	Mother, sister	P	+	+	12	...	3.7	0.2	12	11.7
6	18, M	C	Childhood	Father, brother	P	0	0	12	...	4.6	0.2	3	15.2
7	25, M	N	17	...	I	0	+	15	27	2.6	0.6	4.5	12.0
8	17, M	C	13	Mother, sister, maternal aunt	I	0	0	15	...	2.5	0.2	4.2	18.2
9	26, M	C	Childhood	Mother, sister	I	+	0	17	...	2.3	0.5	2.3	13.5
10	37, M	C	21	...	I	+	+	18	28	2.1	0.3	3.2	14.0
11	67, M	C	67	...	0	+	+	19	26	1.8	0.0	3.1	14.8
12	23, M	C	22	Father	I	+	+	19	26	4.6	0.8	2.2	14.8
13	19, M	C	18	...	I	+	0	20	28	2.2	0.1	0.9	15.2
14	22, M	C	21	...	I	0	0	20	31	2.5	0.1	1.8	16.5
15	28, F	C	28	Son (Case 4)	0	0	0	20	...	0.8	0.3	2.6	14.0
16	26, M	C	21	...	I	+	+	20	27	1.2	0.2	1.2	14.8
17	31, M	C	29	...	I	0	+	22	28	2.2	0.4	3.1	13.1
18	19, M	C	18	...	I	+	0	22	30	2.9	0.3	2.7	17.8
19	23, M	C	20	Daughter, 2 cousins	I	0	0	23	...	1.5	0.1	1.2	13.7
20	23, M	C	21	...	I	0	0	24	28	3.0	0.6	1.1	14.5
x	27, M	C	17	...	I	0	0	33	...	2.0	0.2	1.2	15.3

* Cases 1 through 20 are patients with hereditary non-spherocytic hemolytic disease. Case x is the only patient with constitutional hepatic dysfunction observed during this period.

† Intermittent (I). Persistent (P)

‡ Liver and spleen: Palpable (+) or non-palpable (0)

Bergh reaction. There was no increase in the direct-reacting pigment. The serum total bilirubins ranged from 1.4 to 8 mg. per 100 ml. There was a considerable variation in the degree of hyperbilirubinemia from month to month in the same patient. This did not seem to be related to exertion, diet or alcoholic intake. One patient (Case 7) received 100 mg. of cortisone acetate daily for two weeks without improvement in his bilirubinemia.

Studies of erythrocytic survival were conducted with Cr^{51}-labelled cells in all patients. Only one patient (Case 10) of the total of twenty-one had a normal survival of the tagged cells, permitting the diagnosis of constitutional hepatic dysfunction. The patients with a family history strongly suggestive of hemolytic disease, or with known hemolysis since childhood, demonstrated shortened survival of their own cells which had been transfused. In the patients without a convincing family history of hemolytic disease an intracorpuscular defect was demonstrated by differential red cell survival studies. Normal cells transfused into them survived at the usual rate, while their own tagged cells had a short survival in themselves or in normal recipients or both. There were eleven patients in whom the half-life of the red cell Cr^{51} was between seven and nineteen days and eight patients in whom it was twenty to twenty-four days (normal twenty-seven to thirty-five days).

Liver function studies were performed in all patients. The results of the cephalin-cholesterol flocculation test, thymol turbidity test, alkaline

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BILIRUBINEMIA WITH INDIRECT VAN DEN BERGH REACTION (1955 TO 1959)*

Osmotic Fragility §	Bone Marrow ‖	Liver Biopsy ¶	Cholecysto-gram	Iron (μg./100 ml.)		Symptoms and Miscellaneous
				Serum	Unsaturated Iron-binding Capacity	
N	...	...	Stones	...	...	Splenectomy, age 16 (435 gm.), no clinical improvement; cholecystectomy, age 18; frontal bossing; fatigue, abdominal fullness and loose stools
N	EH	N	N	...	...	Abdominal fullness, recurrent weakness and fatigue, constipation
N*	EH	...	Stones	345	46	Splenectomy, age 8 (170 gm.), mild improvement in anemia following splenectomy; headaches, decreased exercise tolerance, fatty food intolerance, right upper abdominal discomfort; frequent colds
N	EH	...	...	...	...	Weakness, dizziness, occasional loose stools; frequent colds; no clinical improvement with cortisone
N*	EH	...	N	213	259	Splenectomy, age 17 (610 gm.), no improvement; fatigue, nausea, abdominal fullness, weight loss and constipation
N	EH	N*	N	183	18	Fatigue, anorexia, right upper quadrant discomfort
N*	EH	N	N	...	...	Splenectomy, age 25 (340 gm.), no improvement; increased bilirubinemia while receiving steroids; right upper quadrant fullness, intermittent fatigue, anorexia, headaches and constipation
N	...	...	N	...	...	Abdominal fullness, weight loss, fatigue and occasional loose stools.
N	EH	N*	Stones	...	...	Cholecystectomy age 23; nausea, substernal burning and abdominal uneasiness
N	..	N*	...	189	165	Abdominal fullness, weight loss, fatigue and constipation
N*	EH	...	N	...	...	Hypertensive arteriosclerotic heart disease, residuals of cerebral vascular accident
N	EH	N*	N	...	..	Weakness, right upper quadrant discomfort, weight loss and serous macular retinopathy
N	...	N	N	...	..	Headaches, dizziness, fatigue and right upper quadrant distress
N	...	...	...	...	...	Malaise and upper abdominal uneasiness
...	...	...	...	...	..	Asymptomatic; discovered during investigation of Case 4
N	EH	N	N	..	..	Headaches, abdominal distress, loose stools, fatigue, temperomandibular joint pain and frequent colds
N	EH	N	..	..	...	Abdominal uneasiness and loose stools
N	...	...	..	...	...	Fatigue, nausea, loose stools, abdominal uneasiness and substernal burning
N	...	N	..	..	..	Malaise, headache and constipation
N	...	...	...	...	...	Asymptomatic
N	...	N	...	...	...	Abdominal uneasiness, fatigue and constipation

§ Normal red cell osmotic fragility (N). Slight increase in red cell osmotic fragility after incubation at 37°c. for twenty-four hours (N*).
‖ Erythroid hyperplasia (EH).
¶ Normal liver biopsy (N). Histologically normal liver biopsy specimen except for increased hemosiderin within the hepatic cells (N*).

phosphatase, serum albumin and globulin were normal. There was increased retention of bromsulfalein in three patients. Two patients (Cases 11 and 18) had transitorily increased retention of bromsulfalein of approximately 8 per cent. These studies were repeated and less than 5 per cent retention in forty-five minutes was observed in both cases. One patient (Case 12) had a bromsulfalein retention of 18 to 24 per cent in forty-five minutes on repeated occasions during six months of observation. In this patient all other liver function studies and a liver biopsy specimen were within normal limits except for indirect bilirubinemia.

Bone marrow aspirates were obtained in eleven patients. Erythroid hyperplasia of varying severity was demonstrated in each of these specimens. Liver biopsy specimens were obtained from eleven patients by the Vim-Silverman technic. A slight increase in hemosiderin deposition within the parenchymal and Kupffer cells was demonstrated in four patients (Cases 6, 9, 10 and 12). There were no other abnormal findings in any of the biopsy specimens. Serum iron was increased in four patients. The increased iron stores were believed to be due to the increased absorption commonly associated with hemolytic disorders [*61*]. Cholecystograms were performed in twelve patients and cholelithiasis was demonstrated in three (Cases 1, 3 and 9).

Splenectomy had been performed in four patients (Cases 1, 3, 5 and 7) from three months to ten years prior to evaluation at this hospital.

There was questionable improvement in the severity of the anemia in one patient (Case 3), however, all four patients had a persistent, moderately severe, hemolytic process after splenectomy. Pathologic sections from two of the spleens were available. Histologic changes were similar to those previously reported in this disorder [*2,13,14*].

COMMENTS

Most of the reported cases of hereditary non-spherocytic hemolytic disease have been characterized by a brisk hemolytic state [*1–20*]. In our patients the intensity of the hemolytic disease varied from mild to severe. This spectrum of severity is similar to many of the other hemolytic disorders. The patients can be divided into three groups, those with severe hemolysis (Cases 1 through 5), those with moderate hemolysis (Cases 6 through 12), and those with mild hemolysis (Cases 13 through 20).

In the group of patients with moderately severe disease, a definite hemolytic anemia existed. The rate of red cell destruction was so rapid that the patients were unable to maintain a normal concentration of hemoglobin. In this group of patients and others like them, the spleen was usually palpable and reticulocytosis was pronounced. Jaundice was frequently persistent and often first noted in early childhood.

Anemia was not present in the patients with a moderate rate of hemolysis (Cases 6 through 12). The ability of the bone marrow to produce red cells is sufficient to permit the milder hemolytic states to exist without anemia [*57,58*]. Increased numbers of reticulocytes were found in the blood. The spleen was palpably enlarged in half the patients. Jaundice was intermittent.

When hemolysis is mild (Cases 13 through 20) many of the characteristic findings may be absent. Five of these patients had less than 2 per cent reticulocytes in the peripheral blood. Normal fecal urobilinogen values were obtained in several of these patients. The spleen was not palpable in six of the eight patients in this group. Bilirubinemia was absent in one (Case 15).

Although bilirubinemia is the most consistently abnormal laboratory finding in hereditary non-spherocytic hemolytic disease, it is not always a good index of the rate of hemolysis. In uncomplicated hemolytic states bilirubinemia is usually not present until the rate of hemolysis exceeds the normal rate of red cell destruction by two to four times. Up to this point, the excretory mechanism is able to keep abreast with the production of bilirubin without a backlog in the plasma [*57*]. Patients with mild hemolytic disease (Cases 13 through 20) not only had an elevated serum bilirubin but also exhibited levels which frequently exceeded those in patients with pronounced hemolysis (Cases 1 through 13). In several patients (Cases 4, 7, 9 and 12) serum bilirubin levels between 4.5 and 8 mg. per 100 ml. were observed. Bilirubinemia of this degree is unusual in uncomplicated hemolytic states [*58*]. In the absence of demonstrable hepatic disease these findings suggest that there may be a defect in bilirubin metabolism in addition to the intrinsic defect in the red cell. Whether this defect is in the conjugation of bilirubin, in the transport of the pigment, or elsewhere, is not known [*29*].

The striking similarity between our patients with moderate and mild hereditary non-spherocytic hemolytic disease and the reported cases of constitutional hepatic dysfunction makes it difficult to believe earlier investigators could distinguish these disorders without the benefit of red cell survival tests. Even in the recent literature patients with constitutional hepatic dysfunction are described with suggestive evidence of mild hemolysis [*23,25*]. This makes it difficult to evaluate the reported cases of constitutional hepatic dysfunction.

Constitutional hepatic dysfunction was first described in 1901 by Gilbert and Lereboullet [*26*]. Since then several hundred cases and many series of patients have been reported. The first case of hereditary non-spherocytic hemolytic disease was described by Widal and Ravaut in 1902 [*18*]. Descriptions of hereditary non-spherocytic hemolytic disease did not again appear in the medical literature until 1939 [*17*]. Less than one hundred cases have been reported. One would imagine that constitutional hepatic dysfunction is a relatively common disorder and that hereditary non-spherocytic hemolytic disease is relatively rare. However, in the last four years we have seen twenty patients with hereditary non-spherocytic hemolytic disease. During this same time we have established the diagnosis of constitutional hepatic dysfunction only once.

A diagnosis can readily be made in a patient with anemia, bilirubinemia, a marked reticulocytosis and a pronounced abnormality in red cell survival. But what of a patient with mild jaundice, without anemia or reticulocytosis

whose red cells appear normal under the microscope? He may or may not have a compensated hemolytic disease, and unless the survival of his red cells or the rate of red cell production is measured it is impossible to be sure. On the basis of our experience we suspect that many cases have in the past been classified as constitutional hepatic dysfunction when in fact they were hemolytic disease. We believe that hereditary non-spherocytic hemolytic disease is the relatively common disorder and that constitutional hepatic dysfunction is relatively rare. It is proposed that normal erythrocyte survival time be demonstrated before the diagnosis of constitution hepatic dysfunction is considered established.

The diagnosis of hereditary non-spherocytic hemolytic disease is an imprecise one. This is apparent from previous reports of disorders described under this designation which are characterized by peculiarities which permit them to be separated from the type of patient herein described [*61–65*]. Even when such cases are eliminated it is suspected that hereditary non-spherocytic hemolytic disease may not be one disease, but rather a group of hereditary red cell defects which we have not yet learned to identify. The work of Selwyn and Dacie [*66*] demonstrated heterogenicity in hereditary non-spherocytic hemolytic disease. The addition of glucose to the blood in some cases but not in others, prevented autohemolysis. The demonstration of Heinz-body formation, glutathione instability and lack of glucose-6-phosphate dehydrogenase which has been reported to exist in some cases indicates that enzymatic and metabolic lesions may be involved [*20,48,67*].

SUMMARY

Twenty patients with hereditary non-spherocytic hemolytic disease, with varying rates of hemolysis, are described. This familial disorder is characterized by the presence of an intracorpuscular defect of the erythrocytes without definitive morphologic abnormalities. It is important to differentiate this disease from hereditary spherocytosis because splenectomy is of little or no benefit.

When hemolysis is mild, constitutional hepatic dysfunction and posthepatic hyperbilirubinemia may be clinically indistinguishable from hereditary non-spherocytic hemolytic disease. Red cell survival studies are frequently required to establish the appropriate diagnosis. Our incidence of constitutional hepatic dysfunction was surprisingly low when these technics were employed.

The nature of the red cell lesion in hereditary non-spherocytic disease is not known. Recent evidence supports the possibility of an enzymatic abnormality in at least some of the patients. Bilirubinemia, which is out of proportion to the severity of hemolysis, suggests a possible defect in bilirubin conjugation or transport in addition to the intrinsic red cell abnormality.

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Familial Hyperoxaluria*

Report of a Family, Review of the Literature

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In a medical-urologic clinic in which 207 patients were studied over 50 per cent had a demonstrable metabolic abnormality underlying the tendency to the formation of stones [*1*]. Among the patients with a family history of stones in the urinary tract the following causative metabolic diseases were noted: cystinuria, glycinuria [*2*], idiopathic hypercalciuria, hyperuricemia and hyperparathyroidism. Almost half of the families with urolithiasis had no apparent underlying etiology. Elucidation of the metabolic defects involved in these disease states has led to a better understanding of the factors involved in the formation of stones within the urinary tract. However, the metabolic anomaly underlying formation of one of the most common substances comprising urinary calculi, calcium oxalate, has not been adequately investigated [*3*].

The natural history of primary hyperoxaluria was recently described [*4*] as characterized by progressive calcium oxalate urolithiasis, nephrocalcinosis and recurrent urinary tract infections leading to renal parenchymal destruction and death from uremia, occurring either in childhood or in early adult life. The pathognomonic biochemical abnormality is persistently high excretion of oxalic acid over twenty-four hour urinary collection periods.

This report describes three siblings with hyperoxaluria and recurrent renal calculi. Metabolic studies were performed, including attempts to lower the excretion of urinary oxalic acid.

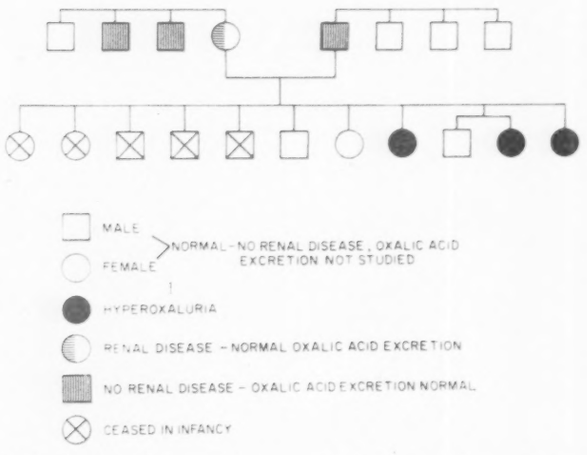


FIG. 1. Geneology of hyperoxaluric family reported on herein.

METHODS

The method of determination of oxalic acid in the urine was adapted from that of Archer et al. [*5*]. Ten ml. concentrated hydrochloric acid were placed in a urine collection bottle and a twenty-four hour urine sample obtained. An aliquot of 200 ml. filtered urine was adjusted to pH 5 to 5.5, the urine was poured into a graduated cylinder, and divided in equal portions between two 200 ml. centrifuge bottles for duplicate analyses. Four ml. of 5 per cent $CaCl_2$ were added to each bottle and the contents mixed. After standing overnight at room temperature, the bottles were centrifuged. Without disturbing the precipitated calcium oxalate, as much as possible of the supernatant was removed by suction. The precipitates were transferred quantitatively to 30 ml. test tubes with several 2 ml. washings with water. The tubes were centrifuged and the supernatants decanted. The precipitates were stirred by tapping the tubes, then washed twice with 4 ml. portions of 2 per cent ammonia. The tubes were allowed to drain in an inverted position. The precipitates were then dissolved in 2 ml. 1N sulfuric acid in 80°C. water bath and titrated with 0.01N or 0.1N potassium permanganate, depending on the quantity of oxalate present.

CASE REPORTS

CASE 1. M. T., a fourteen year old Puerto Rican girl, was first seen at the Mount Sinai Hospital on

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FIG. 2. Section of kidney from one patient (Case I) demonstrating tubular deposit of calcium oxalate crystals. Original magnification × 410.

December 12, 1956. She complained of gross hematuria which had first occurred three months prior to admission; it lasted for two days at that time, and had recurred one day prior to admission. There was no history of fever or pain. The patient's mother and two of her sisters were known to have had renal calculi; two brothers and one sister were asymptomatic; five siblings died in infancy of unknown causes. (Fig. 1.)

Physical examination revealed a normotensive afebrile girl in apparent good health. The abnormal findings were limited to tenderness in the left costovertebral angle and a well delineated non-tender moveable mass, about 12 cm. in diameter, in the left upper quadrant of the abdomen.

The urine was alkaline, specific gravity 1.006, protein 3 plus. The sediment contained 25 red blood cells per high power field and many calcium oxalate crystals. The blood count was normal. The serum calcium, phosphorus, and the twenty-four hour urinary calcium excretion on a low calcium (Bauer-Aub) diet were all normal. The blood urea nitrogen was 10 mg. per cent.

Intravenous pyelography demonstrated prompt excretion on the right, and small clusters of round calcifications within the contour of the right kidney. The left kidney was enlarged, gave no indication of excretory function, and contained a large staghorn calculus. Bleeding from the left ureteral orifice was seen at cystoscopy.

A left nephrectomy was performed on January 8, 1957. The specimen revealed nephrolithiasis, marked hydronephrosis, and acute and chronic pyelonephritis. Tubular deposits of calcium oxalate were demonstrated on histological examination. (Fig. 2.) The stone was not analyzed chemically.

TABLE I

TWENTY-FOUR HOUR URINARY OXALIC ACID EXCRETIONS OF HYPEROXALURIC SIBLINGS

Case I (M. T.)		Case II (C. T.)		Case III (A. S.)	
Date	Urinary Oxalic Acid Excretion (mg. dihydrate per 24 hr.)	Date	Urinary Oxalic Acid Excretion (mg. dihydrate per 24 hr.)	Date	Urinary Oxalic Acid Excretion (mg. dihydrate per 24 hr.)
9/29/58	82	10/16/58	94		
10/1/58	80	10/21/58	77	11/13/58	102
10/2/58	97	10/26/58	63	11/14/58	182
10/13/58	153	11/2/58	150	11/15/58	175
10/15/58	77	11/4/58	51	11/16/58	99
10/20/58	82	11/9/58	136	11/17/58	4
10/21/58	79	11/13/58	75	11/18/58	2
10/26/58	56	11/16/58	11	12/30/58	175
11/2/58	34	11/17/58	92	...	...
11/3/58	126	11/24/58	178	...	...
11/9/58	116	11/30/58	111	...	...
11/13/58	87	12/7/58	131	...	...
11/17/58	92	12/11/58	210	...	...
11/24/58	262	12/17/58	136	...	...
11/30/58	122	12/22/58	117	...	...
12/7/58	138	3/13/59	127	...	...
12/4/58	86	...	...	...	...
12/17/58	166	...	...	...	...
12/22/58	111	...	...	...	...
3/13/59	114	...	...	...	...

She was discharged and remained asymptomatic until March 1958, when she began to notice infrequent pain in the right flank and intermittent hematuria. There was no fever, dysuria or frequent urination. Serial intravenous pyelograms demonstrated dilatation of the upper calyceal system and enlarging calculi in the remaining kidney.

The patient was readmitted to the hospital on September 3, 1958. Physical examination was noncontributory. The urine specific gravity was 1.014, reaction acid, protein 1 plus. The sediment contained 2 to 5 red blood cells per high power field, many white blood cells and calcium oxalate crystals. No cystine or uric acid crystals were seen. The blood urea nitrogen was 12 mg. per cent. The serum electrolytes were normal, as were albumin, globulin, calcium, phosphorus and alkaline phosphatase. The serum uric acid, on two determinations, was 6.8 and 5.8 mg. per cent. The twenty-four hour urinary calcium excretion ranged from 65 to 96 mg. on a low calcium diet. Simultaneous creatinine and phosphate clearances indicated 93.5 per cent tubular reabsorption of filtered phosphate. Bromsulphalein retention was normal. Paper chromatography did not demonstrate abnormal cystinuria or other aminoaciduria. The twenty-four hour urinary oxalic acid excretion, while she was taking a general diet (with foods rich in oxalate excluded), was persistently increased. (Table I.) The excretion ranged from 77 to 153 mg. per

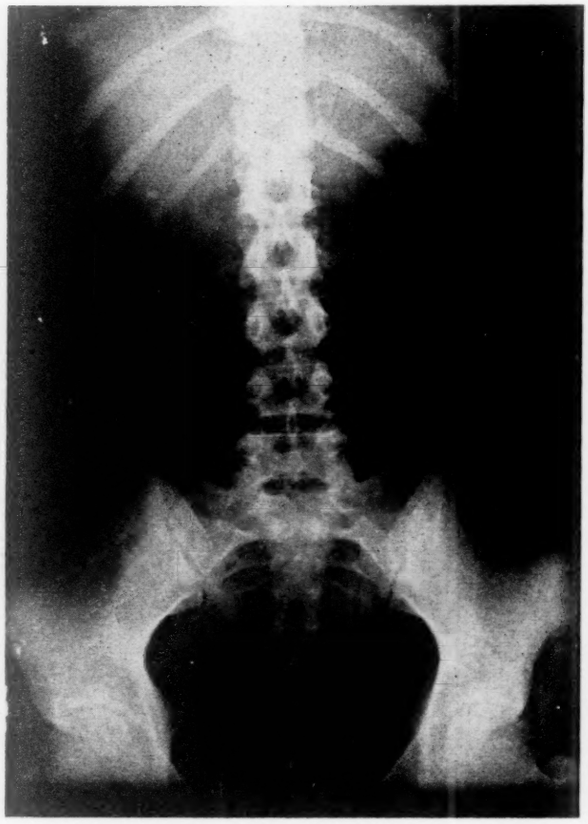


FIG. 3A, abdominal roentgenogram in Case I demonstrating small renal calculus in upper pole of right kidney. Taken on February 1957.



FIG. 3B, abdominal roentgenogram taken two years later in the same patient demonstrating enlargement of right renal calculus and several new calculi.

twenty-four hours (normal range, 20 to 40 mg. per twenty-four hours).

Abdominal roentgenograms demonstrated further increase in the size of the calculi. (Fig. 3.) Roentgenograms of the skeleton, and of the lamina dura, were normal. Ophthalmologic examination, including slit lamp examination, revealed no crystals in the corneal limbus. No oxalate crystals were seen on either bone marrow aspiration or biopsy.

Sodium benzoate, 20 gm. daily in divided doses, was administered orally for thirty-three days, from October 19, 1958 to November 21, 1958. During this period the excretion of oxalic acid first was reduced to normal, and then "escaped" with a "rebound" to levels above the baseline. (Fig. 4.) Following this, pyridoxine was given in a dose of 300 mg. per day for eleven days. This did not influence the excretion of oxalic acid (*vide infra*). Then a high calcium diet with 6 gm. of calcium gluconate supplement per day was given for twenty-two days, attempting to reduce soluble oxalate absorption from the intestine. This also did not influence the excretion of oxalic acid. At discharge, the twenty-four hour excretion of oxalic acid in the urine was 166 mg.

During her hospital course she had received antibiotic treatment for her urinary tract infection. She was discharged on December 23, 1958, and advised to avoid foods rich in oxalate, to maintain a high fluid intake, and to return to the clinic for further management of her urinary tract infection.

CASE II. C. T. (M. T.'s older sister) was admitted to the Mount Sinai Hospital on July 6, 1948, at nine years of age, with a bilateral bronchopneumonia. Physical examination revealed no abnormalities. The urine sediment contained 10 to 15 red blood cells per high power field and many calcium oxalate crystals. The blood urea nitrogen was 8 mg. per cent, the serum calcium and phosphorus were normal.

Six weeks later, long after the pneumonia had cleared, the patient had an episode of painless gross hematuria. Intravenous pyelography demonstrated a normal left kidney and ureter. The right calyces were dilated, and there were radiopaque calculi at the right ureteropelvic junction and within the right renal pelvis. A right nephrectomy was performed on August 31, 1948. A large hydronephrotic kidney with little cortical tissue and a dumbell shaped stone at the ureteropelvic junction were found. The stone was not analyzed. Microscopic examination revealed no nephrocalcinosis.

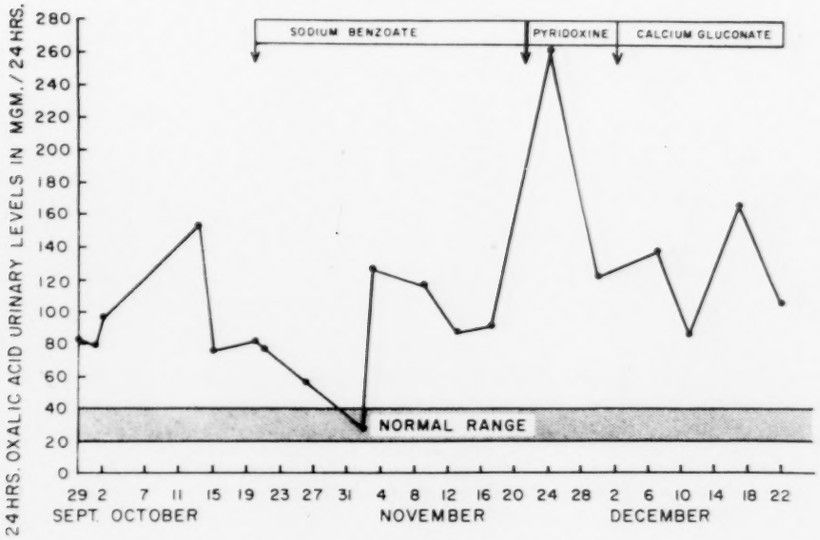


FIG. 4. Urinary oxalic acid excretion in Case I.

She was seen periodically from 1951 to 1958, receiving treatment for bronchial asthma, and had no urinary symptoms during this period. She was readmitted for study on October 14, 1958 (after her sister had been found to have hyperoxaluria). She now had emphysema of the chest, and there were bilateral expiratory wheezes, but no other abnormalities were noted on physical examination. The blood count was normal. The urine had a specific gravity of 1.030, was acid, and contained a trace to 2 plus protein. The sediment contained 2 to 4 red blood cells per high power field and many calcium oxalate crystals. The blood urea nitrogen was 15 mg. per cent, the serum electrolytes, calcium, phosphorus, albumin, globulin and alkaline phosphatase were all normal. The serum uric acid was 4.9 mg. per cent. Bromsulphalein retention was normal. The urinary calcium excretion was normal on a low calcium diet.

The remaining kidney and ureter were normal on intravenous pyelography; no calculi were seen. Ophthalmologic examination and bone marrow aspiration were negative for crystals. The urinary oxalic acid was found consistently to be in excess of the normal (Table I); the maxium excretion was 210 mg. per twenty-four hours. She was treated consecutively with a low oxalate diet, sodium benzoate, pyridoxine, and calcium gluconate supplement to a high calcium diet. The results were similar to those obtained in Case I. (Fig. 5.) She was discharged on December 23, 1959, on a low oxalate, high fluid intake.

CASE III. A. S. (M. T.'s older sister) was admitted to the Mount Sinai Hospital on December 3, 1949, at fourteen years of age. She complained of colicky right renal pain, dysuria, urgency and frequency of urination, gross hematuria, and a temperature to 101°F. Physical examination revealed only tenderness in the right costovertebral angle. The urine sediment contained 3 to 5 red blood cells per high power field and many calcium oxalate crystals. Intravenous pyelography demonstrated a normal left kidney and bladder, but no excretory function of the right kidney. A small radiopaque density was thought to represent a right ureteral calculus. The blood urea nitrogen was 25 mg. per cent; serum calcium and phosphorus were normal.

A purulent efflux from the right ureteral orifice was noted at cystoscopy. There was an obstruction to the passage of a catheter at the lower end of the right ureter. Two days later a catheter was successfully passed into the right ureter and left in place for two days. Repeated intravenous pyelography then demonstrated excretory function on the right, with a small calculus in the right ureter. The patient's symptoms

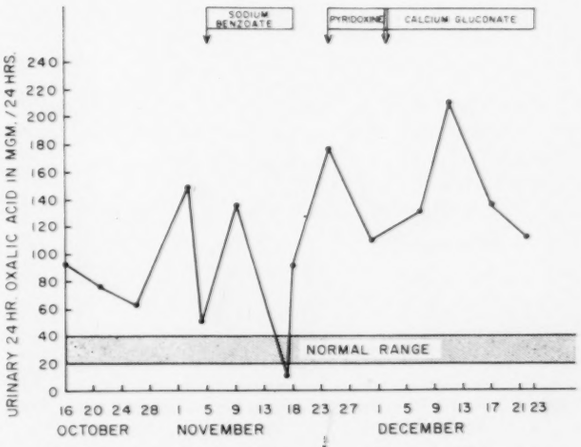


FIG. 5. Urinary oxalic acid excretion in Case II.

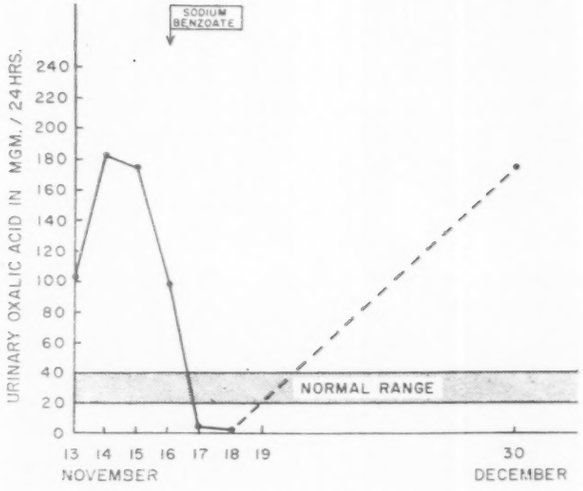


FIG. 6. Urinary oxalic acid levels in Case III.

subsided and she passed the stone spontaneously several days after discharge.

She returned to the hospital for study following the discovery of hyperoxaluria in her siblings. Serial abdominal roentgenograms had revealed no abnormalities, and save for occasional pain in the left flank she had been asymptomatic in the interval.

The physical examination was non-contributory. The urine specific gravity was 1.030, reaction acid, protein 1 plus, with many red blood cells and calcium oxalate crystals in the sediment. The blood count was normal. The blood urea nitrogen was 11 mg. per cent, and serum uric acid 4 mg. per cent. The serum calcium, phosphorus and alkaline phosphatase were normal. Twenty-four hour urinary calcium excretion on a low calcium diet was normal. Hyperoxaluria was demonstrated; this responded strikingly to the administration of sodium benzoate. (Fig. 6.)

The patient was discharged six days following admission, and one month later her oxalic acid excretion was 175 mg. per twenty-four hours. She is asymptomatic, and has been advised to continue a large fluid intake and a low oxalate diet.

CASE IV. R. T., a fifty-eight year old Puerto Rican woman (the mother of M. T., C. T. and A. S.), was admitted to the hospital in February 1957, for a left ureteral stone. Ureteral catheterization revealed hydronephrosis. The stone was passed spontaneously. It was not analyzed. In June 1958, a small radiopaque stone was seen in the lower pole of the right kidney.

She was readmitted on October 18, 1958, for investigation of recurrent calculi. The physical examination was within normal limits. The blood count was normal. The urine specific gravity was 1.010 and the sediment was normal. The blood urea nitrogen, serum calcium, phosphorus and alkaline phosphatase were all normal. Three twenty-four hour urine specimens revealed normal oxalic acid excretion, the values being 17, 11 and 16 mg. (Table II.)

TABLE II
TWENTY-FOUR HOUR URINARY OXALIC ACID EXCRETIONS IN ELEVEN CONTROL SUBJECTS (FOUR ADDITIONAL MEMBERS OF THE PATIENTS' FAMILY INCLUDED)

Data	Urinary Oxalic Acid Excretion (mg. dihydrate per 24 hr.)*
Case IV R. T., mother	
10/14/58	17
10/21/58	11
10/27/58	16
E. T., father	
3/13/59	0.4
3/20/59	0.8
3/25/59	8.0
P. A., maternal uncle	
5/8/59	2.0
P. A. A., maternal uncle	
6/2/59	29.0
Control subjects	
C. R.	20.0
M. M. (renal stone)	14.0
M. A. (renal stone)	23.0
J. B. (renal stone)	13.0
R. M. (chronic glomerulonephritis)	10.0
M. F. (renal stone)	2.0
J. R. (renal stone)	14.0

* Range for this laboratory is 0.4 to 29 mg. per twenty-four hours.

Comment. This is, then, a family in which three female siblings have urolithiasis and hyperoxaluria. None of eight other siblings were said to have kidney disease, although they were not examined. The mother also has nephrolithiasis, but both parents and two maternal uncles were found to have normal urinary oxalate levels.

Calcium oxalate deposits were demonstrated within the tubules of one kidney removed surgically. The urinary oxalic acid excretion of the patients described diminished markedly in response to sodium benzoate therapy (Figs. 4, 5, and 6) but this response was shortlived despite continued administration of the drug. Neither pyridoxine nor calcium influenced the hyperoxaluria.

COMMENTS

The disorders of oxalic acid metabolism consist of two clinical entities, oxalosis and hyper-

TABLE III

PATIENTS WITH OXALOSIS WITHOUT DOCUMENTED HYPEROXALURIA

Author	Sex of Patient	Age at Onset of Symptoms (yr.)	Age at Death (yr.)	Urolithiasis	Nephrocalcinosis	Extrarenal Oxalate Deposits	Renal Failure	Family History of Stones	Remarks
Lepoutre [8]	?	4	...	+	+	?	?	?	Short report; renal biopsy revealed interstitial calcifications; case report not well documented
Vischer [58]	M	10	11	0	+	?	+	0	...
Davis [6]	M	3	12	+	+	+	+	?	First well documented case in the literature
Ostry [59]	M	21	24	+	+	?	+	?	Author reports another case probably not oxalosis; this case may not be oxalosis
Mulloy [60]	M	4 mo.	5 mo.	0	+	?	+	?	May not be oxalosis
Chou and Donohue [61]	M	2	7	+	+	+	+	+	Father had renal stone
Zollinger and Rosenmund [62]	M	3	4	0	+	+	+	?	Author reports on two other adults with nephrocalcinosis, probably not oxalosis
Burke et al. [48]	M	3	11	+	+	+	+	?	...
Dunn [65]	F	4	15	+	+	+	+	+	Father had renal stone
Neustein et al. [64]	M	1	4	+	+	+	+	+	...
Arons et al. [65]	M	5	24	+	+	+	+	?	...
Lund and Reske-Nielson [66]	F	17	36	+	+	+	+	0	Unusual cases, patients lived to fourth and fifth decades
Lund and Reske-Nielson [66]	F	35	40	+	+	+	+	0	...
DeToni et al. [67]	M	Birth	11	+	+	+	+	0	...
Edwards [68]	M	35	11	+	+	+	+	+	Siblings, maternal uncle had kidney stones
Edwards [68]	M	23	23	0	+	+	+	+	...
Simko [69]	?	1	3	+	+	+	+	0	...
Nieman et al. [70]	F	3 mo.	5 mo.	0	+	?	+	0	May be oxalosis
Oigaard and Soderhelm [71]*	F	13	13	?	?	?	?	+	...
Oigaard and Soderhelm [71]	M	17	17	0	+	0	+	+	...
Oigaard and Soderhelm [71]	M	25	27	+	+	+	+	+	Thyroid was the only extrarenal tissue with calcium oxalate deposits at postmortem examination
Oigaard and Soderhelm [71]	M	26	...	+	?	?	0	+	Still alive

* The patients reported on by Oigaard and Soderhelm were siblings.

oxaluria. The relation of the one to the other is not altogether clear. Oxalosis has been viewed as an inborn error of metabolism characterized by the deposition of oxalate crystals in the kidneys and other organs, with death ultimately resulting from renal failure [6]. The syndrome of primary hyperoxaluria is characterized by increased excretion of oxalates in the urine, leading to the formation of renal stones, pyelonephritis and, ultimately, to renal failure. The viewpoint of Archer et al. is that hyperoxaluria and oxalosis are reflections of the same underlying defect in the metabolism of oxalic acid [4]. They suggest that excessive formation of oxalate leads to a high concentration of this ion in body fluids, resulting both in excessive urinary concentrations of oxalate, or hyperoxaluria, and deposition of oxalate crystals throughout the body, or oxalosis. An alternative viewpoint is that primary hyperoxaluria and generalized oxalosis are entirely different entities, the former the result of a renal "leak," similar to that described in certain aminoacidurias [7], the latter due to a generalized inborn error of metabolism and involving a secondary hyperoxaluria resulting from the vastly increased total body pool of oxalate. They would thus bear the same relationship to each other as cystinuria, in which there is no generalized disturbance of cystine metabolism but only a renal leak, and cystinosis, consisting of a generalized defect with inability to metabolize cystine, one manifestation of which may be secondary hypercystinuria [7].

Oxalosis, first described in 1925 [8], is characterized by the findings, usually early in life, of progressive renal failure, calcium oxalate urolithiasis, oxalate nephrocalcinosis, and extrarenal deposition of calcium oxalate in the liver, spleen, heart muscle, bone marrow and other organs [4,6]. Antemortem diagnosis of oxalosis depends on the demonstration of the characteristic crystals in liver biopsy specimens or bone marrow aspirates. Twenty-two cases of oxalosis collected from the literature are reviewed in Table III. In no case was the diagnosis documented until the postmortem findings were

TABLE IV
PATIENTS WITH HYPEROXALURIA

Author	Sex of Patient	Age at Onset of Symptoms (yr.)	Age at Death (yr.)	Urolithiasis	Nephrocalcinosis	Extrarenal Oxalate Deposits	Renal Failure	Family History of Stones	Urine Oxalic Acid (mg./24 hr.)	Remarks
Newns and Black [57]	F	2	...	+	?	?	+	+	95 to 182	Child still alive at age 5; older brother had died of renal failure with calcium oxalate stones at age 8
Aponte and Fetter [36]	M	5	16	+	+	+	+	+	200	Identical
Aponte and Fetter [36]	M	10	13	+	+	+	+	+	130	Twins
Aponte and Fetter [36]	M	7	9	+	+	+	+	+	?	Sibling of aforementioned two patients; twenty-four hour urine oxalic acid not measured
Archer et al. [4]	M	1	...	+	?	?	+	0	162 to 290	Alive at age 22
Archer et al. [4]	F	4	...	+	+	?	0	0	110 to 262	Alive at age 11
Godwin et al. [72]	M	5	10	+	+	+	+	+	130 to 180	Probably same patient as reported on by Dempsey [73], who gives no data other than the same oxalic acid excretion
Hodgkinson [74]	M	8	...	+	?	?	?	?	230	Alive at age 32
Daniels, Michels, Aisen and Goldstein (1960)*	F	14	...	+	0	?	0	+	262	Alive at age 17
	F	9	...	+	0	?	0	+	210	Alive at age 20
	F	14	...	+	0	?	0	+	182	Alive at age 24
Myers [75]†	F	?	?	+	?	?	?	+	?	All said to have hyperoxaluria; no urinary levels given
Myers [75]	F	?	?	+	?	?	?	+	?	...
Myers [75]	M	?	?	+	?	?	?	+	?	These cases studied by Archer [56] were said to have normal urinary oxalic acid levels.
Myers [75]	?	?	?	+	?	?	?	+	?	

* The patients in the study by Daniels et al. were siblings.
† The patients in the study by Myers [75] were siblings.

reviewed. Some cases reported as oxalosis do not fulfill the criteria for diagnosis, as we know it today. In none of these was the urinary excretion of calcium oxalate measured. Extrarenal deposition of calcium oxalate was demonstrated in only thirteen cases. In the remainder, the deposition of these crystals was not mentioned, or the patient was still alive at the time of the report; thus the diagnosis could not be validated.

Ten patients with documented hyperoxaluria, including those in the present report, are summarized in Table IV. In another five patients, included in the table, hyperoxaluria was suspected, although urinary levels were not reported or not measured. Two families previously reported on had hyperoxaluric children with urolithiasis, although in only one of these were the urinary oxalic acid levels stated.

Four of the patients listed as having hyperoxaluria had oxalosis with proved extrarenal deposits of calcium oxalate. These are the only cases of oxalosis known to have been investigated for hyperoxaluria. Thus it remains unclear whether hyperoxaluria invariably accompanies oxalosis, and whether these two disorders are different facets of some underlying metabolic defect or represent two fundamentally distinct clinical entities.

Metabolism of Oxalic Acid. Little has been proved about the origin of body oxalate, although there has been much speculation regarding oxaligenesis. Oxalic acid precursors may be classified as oxaliphores, those foods in which oxalate is preformed as the sodium or calcium salt, and oxaligenes, substances serving as precursors of endogenous oxalic acid [9].

Exogenous Sources of Oxalate. The oxalic acid content of various foods has been tabulated [3]. Chocolate, cocoa, tea, spinach, swiss chard, beet tops, rhubarb and lamb quarters contain large quantities of soluble oxalates. Studies of normal subjects show that ingestion of rhubarb can double urinary excretion of oxalic acid [10]. In British troops in India, large numbers of oxalate stones were found in association with hyperoxaluria, as evidenced by increased excretion of calcium oxalate crystals in the urine. This was attributed to increased use of foods of high oxalate content, as well as to the dehydrating effects of the climate [11]. The wave of oxalate stones in Europe following World War I also was attributed to excessive ingestion of certain green vegetables [12].

However, recent studies have cast doubt on the importance of exogenous oxalate in the pathogenesis of oxalate urolithiasis. The administration of sodium oxalate to normal and hyperoxaluric subjects resulted in the same augmentation of oxalate excretion in each, which was directly proportional to the increase in dietary oxalate [*13*].

There are also reports of increased quantities of oxalate crystals in the urinary sediment, which may be a manifestation of hyperoxaluria, in certain parasitic infestations. Schistosomiasis, giardiasis, amebiasis and ascariasis have been implicated [*14,15*]. It has been postulated that a toxin elaborated by these parasites diminishes the "oxalolytic" action of the liver. Others have suggested that a source of exogenous oxalic acid arises from fermentation in the intestine by colon bacilli [*16*], certain strains of which are known to produce oxalic acid *in vitro* [*17*].

Endogenous Sources of Oxalate. The importance of endogenously formed oxalate is shown by the observation that animals and men on oxalate-free diets and during periods of starvation continue to excrete oxalate in the urine [*3*].

The early literature contains many studies implicating carbohydrates as the most important precursors of oxalate [*18–22*]. In normal subjects, the levels of oxalate in the blood parallel the levels of glucose after oral administration of glucose [*23*]. Patients who had uncontrolled diabetes were found to have hyperoxalemia with reduction of the hyperoxalemia after insulin injection [*23*]. In animals, adrenalin and pancreatectomy produced hyperoxaluria [*19*]. Intravenous administration of glucose in rabbits caused a rise in blood oxalate levels [*21*].

In patients with hepatic disease, hyperoxalemia and hyperglycemia have been noted, and it has been postulated that oxalemia in such patients is a manifestation of diminished glycogenesis [*24*].

The metabolic pathways involved in the formation of oxalate from glucose are not known. That such pathways exist has been shown in a study in which uniformly C^{14}-labelled glucose was fed to a guinea pig, with recovery of a small amount of C^{14}-labelled oxalate from the urine [*25*]. A possible pathway is: glucose → pyruvate → acetaldehyde ($+CO_2$) → glycolic acid → glyoxylic acid → oxalic acid [*26*]. However, glycolic and glyoxylic acids were fed to animals without influencing urinary oxalate. The significance of the older studies which have been cited, unfortunately, is limited by the methods used for determination of blood and urinary oxalate concentrations, which are now considered inaccurate.

There is evidence from the study of microbial metabolism to incriminate two intermediates of the Krebs tricarboxylic acid cycle as precursors of oxalate [*27*]. By hydrolytic cleavage, oxaloacetic acid and oxalosuccinic acid may each give rise to oxalic acid. The importance of these reactions in mammals has not been determined.

Certain amino acids may serve as oxalate precursors. The ingestion of glycine and aspartic acid may produce hyperoxalemia in animals [*28*], and protein restriction will reduce oxalate excretion. Glyoxylic acid, an intermediate of glycine metabolism, has been shown to be converted to oxalic acid in animals and *in vitro* [*13*]. The feeding of C^{14}-labelled glycine results in prompt excretion of labelled oxalate in both normal and hyperoxaluric subjects [*29,30*]. It has been suggested that the defect in hyperoxaluria lies in a failure normally to degrade glycine via glyoxalate to formate and carbon dioxide, with increased operation of the alternate pathway leading to oxalate formation [*29*]. (Fig. 7d.) A defect in the glyoxalate dehydrogenase (e) or glyoxalate transaminase (c) system has also been postulated [*29*]. These are unlikely as primary defects, as metabolic errors are not known to involve increased enzyme activity. A more plausible explanation would be an enzyme deficiency or block in the alternate metabolic pathways of glycine (a) or glyoxylic acid (b) causing hyperoxalemia. (Fig. 7.)

The feeding of large doses of sodium benzoate to hyperoxaluric patients temporarily reduces urinary excretion of oxalate [*13*]. This has been confirmed in the present study. No changes in oxalate excretion were found in control subjects given benzoate. It is likely that the action of sodium benzoate is to condense with glycine (benzoate → benzoyl CoA; benzoyl CoA + glycine in the presence of glycine N-acylase → hippuric acid) to form hippuric acid, thus reducing the available pool of glycine [*32*].

Several studies have related the metabolism of purine and pyrimidine to oxalate production. Dogs fed uracil excreted increased urea, oxaluric acid and oxalic acid. The metabolic pathway in this experiment might be: uracil → isobarbituric acid → isodialuric acid → oxaluric acid → urea + oxalic acid [*33,34*]. It has also

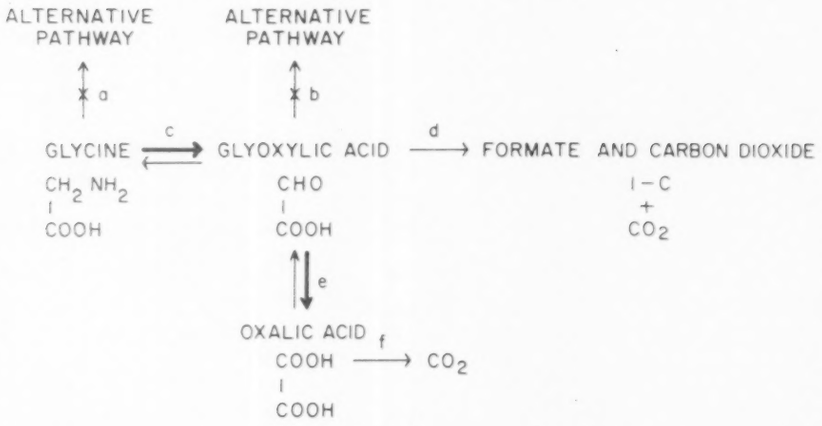


FIG. 7. Proposed scheme of possible inborn errors of metabolism in the pathogenesis of oxalosis and hyperoxaluria.

been suggested that uric acid might give rise to oxalic acid through the action of enzymes of the bacterial flora of the gut, via the following reactions: uric acid → alloxan → alloxanic acid → oxalylurea → urea + oxalic acid [*35*]. The occurrence of hyperuricemia with hyperoxaluria in one case [*36*] is probably fortuitous, and on the basis of renal insufficiency.

Acute pyridoxine deficiency in cats results in oxalate nephrocalcinosis [*37*], perhaps due to decreased activity of the pyridoxine-dependent transaminase system: glycine + ketoglutaric acid → glyoxylic acid + glutamic acid. In this respect it is interesting that in diabetic patients, in whom there is a predisposition to hyperoxaluria and hyperoxalemia [*21,24*], increased excretion of xanthurenic acid is displayed following tryptophane loading [*38*], which is markedly reduced by the administration of pyridoxine. No effects of the administration of pyridoxine on hyperoxalemia were demonstrable in the present study.

The role of ascorbic acid in the formation of oxalate has attracted interest in recent years. Ascorbic acid labelled in its carboxyl carbon with C^{14} has been shown to be converted to labelled urinary oxalate in man [*39*], guinea pig [*25*] and rat [*40*], presumably through the intermediate formation of its oxidized products, dehydroascorbic acid and 2,3-diketo-L-gulonic acid. Although it is known that carbon atoms 1 and 2 of ascorbic acid contribute to the formation of oxalate, the specific mechanisms involved are not yet clear. Cleavage of ascorbic acid under mild chemical conditions to form oxalate and threonic acid can be readily demonstrated [*41–43*]. However, attempts to show formation of oxalate from ascorbic acid in the tissues of rats and guinea pigs *in vitro* have not been successful [*44,45*].

Conversion of ascorbic acid to oxalate may account for the major part of the endogenous urinary oxalate excreted by normal man, but probably not the increased amounts found in the urine of patients with hyperoxaluria. The amount of oxalic acid which can be formed in man from L-ascorbic acid appears to be limited, since the administration of ascorbic acid in doses of 4 gm. per day to human subjects resulted in no significant increase in the excretion of oxalate [*46*]. Doses as high as 9 gm. per day of the vitamin produced an increase of only about 60 mg. per day of oxalate over the control values [*46*].

Extrarenal Fate of Oxalic Acid. Studies with administered C^{14}-labelled oxalate indicate that less than 0.4 per cent of the label appears in expired CO_2, the great bulk of it being excreted, primarily as unaltered urinary oxalate [*29,40*]. Some oxalic acid is also excreted in the bile [*31*]. The small amount of C^{14}-labelled carbon dioxide found after injection of C^{14}-labelled oxalate could be explained by the action of intestinal flora on oxalate excreted through the biliary tree [*47*].

The mechanisms involved in the renal excretion of oxalate are not well understood. A pathologic increase in the concentration of oxalate in the urine could result from either an increased renal clearance or an abnormally high blood level, or both [*48*]. The possibility that oxalate is formed within the urinary tract

itself from metabolic precursors seems less likely [*4*]. Furthermore, primary hyperoxalemia might cause deposition of renal tubular oxalate and excretory abnormalities, or an initial hyperoxaluria could conceivably produce tubular deposits with renal malfunction and a secondary retention of oxalate and elevation of blood levels. A final answer awaits the development of more satisfactory methods of measuring oxalate in the blood.

Factors other than urinary oxalate and calcium concentrations affect the formation of oxalate stones. The ionic strength of the urine influences the solubility of calcium oxalate by the so-called "salting-in" phenomenon [*49*]. For example, calcium oxalate monohydrate is more than three times as soluble in physiologic salt solution as in distilled water [*50*]. *In vitro* studies demonstrate increased solubility of calcium oxalate in the presence of magnesium [*51*]; magnesium oxalate is much more soluble than calcium oxalate and tends to form supersaturated solutions [*50*]. In this regard, it is interesting that magnesium-deficient diets in animals produce calcium oxalate urolithiasis [*52*]. Citrate forms a soluble complex with calcium ion, thus decreasing its activity and tending to prevent precipitation of calcium oxalate. Finally, colloidal phenomena may affect the precipitation of calcium oxalate, although it appears that these are more important in the formation of calcium phosphate stones [*51*].

In experimental animals, vitamin A and D deficiency seems to augment the formation of calcium oxalate stones [*53*].

Several types of oxalate crystals have been described [*54*]. In addition to the usual octahedral form, there are tabloid, spheroid and dumbell forms. The octahedral form is said to be an uncommon nidus of calculus formation, the others showing greater tendency to fusion and coalescence.

Genetic Aspects. In a study of five generations of a family in which calcium oxalate stones occurred with great frequency, the inheritance seemed to follow the pattern of a Mendelian dominant trait which expressed itself almost exclusively in males [*55*]. In a study of the families of three patients with proved hyperoxaluria, no increased oxalate excretion could be demonstrated in any other family member [*4,56,57*]. Normal urinary oxalate levels were found in four relatives of the three hyperoxaluric subjects in the present study. One of these relatives (Case IV) is known to have nephrolithiasis, indicating the danger in assuming that, in a relative of a patient with oxalosis, urinary calculi imply hyperoxaluria. Several cases of oxalosis in twins have been reported. (Tables III and IV.)

Oxalosis has previously been noted more often in males, but if the patients in this report are considered, hyperoxaluria is equally common in males and females.

With the scant case material available to date, no conclusions can be drawn as to the genetic mechanisms involved in the diathesis of oxalic acid.

CONCLUSIONS AND SUMMARY

Primary hyperoxaluria, a recently described disease, is characterized by progressive calcium oxalate urolithiasis, nephrocalcinosis, recurrent urinary tract infections, and death from renal insufficiency at an early age. The characteristic biochemical abnormality is a persistently high urinary oxalate concentration. The essential difference between hyperoxaluria and oxalosis is the extrarenal deposition of calcium oxalate crystals in the latter, but whether they are independent entities or different stages in development of the same disease remains undecided.

Three siblings with hyperoxaluria and urolithiasis were studied. The hyperoxaluria diminished markedly in response to the administration of sodium benzoate, confirming earlier studies, but the response was short-lived despite continuation of therapy. This finding supports the suggestion that glycine is a precursor of at least some of the oxalate in hyperoxaluric subjects.

Pyridoxine administration had no effect in hyperoxaluria. The feeding of soluble calcium salts in an attempt to reduce oxalate absorption by the formation of insoluble calcium oxalate salts in the bowel also was without effect.

The metabolism of oxalic acid is discussed. Recent evidence points to a protein source of endogenous oxalic acid in hyperoxaluria, although ascorbic acid may also serve as an oxalate precursor. Whether the increased renal excretion of oxalate in hyperoxaluria is due to increased blood levels or to a primary renal defect with increased oxalate clearance remains a subject for future investigation. The possibility that "oxalic acid diathesis" is another inborn error of metabolism is considered.

ADDENDUM

Since this paper was prepared, Crawhall et al. have reported on the feeding of 1-C^{13}-labelled glycine to four patients with hyperoxaluria. They conclude that at least the carboxyl carbon atom of glycine was incorporated into the urinary oxalate, and that the carbon skeleton of about one-third to one-half of the urinary oxalate was derived from the carbon skeleton of glycine in these patients [*76*]. In a normal subject, about 40 per cent of the urinary oxalate was derived from glycine, as measured by the same technic [*77*].

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Review

The Design and Analysis of Isotope Experiments*

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WHEN one considers the complexity of the animal organism, the multitude of reactions occurring simultaneously, the variety of chemical dissociations and recombinations, and of syntheses and destructions incessantly taking place, and the shifting of metabolites from one tissue to another, one must marvel at the mechanisms whereby body fluids and tissues maintain their constant chemical composition. This very constancy precludes study of the dynamic state by simple chemical determinations of tissue constituents. A new approach to such a study became available with the use of labeling agents, particularly radioactive isotopes, since they could be prepared in negligible, even chemically non-detectable quantities associated with large amounts of radiation. It is not necessary to dwell upon the fact that the application of tracers to biological problems has produced great advances in the conceptual schemes concerning animal metabolism but it still appears desirable to point up the equally great hazards of obtaining the wrong information from an isotope experiment inadequately interpreted.

A few decades ago the idea that many substances in the animal body exist in a state of continual flux was novel. This concept has now been broadened to include the conversion of a compound in the body, wholly or in part, to almost any other substance composed of the same elements. Therefore, the mere change of part of one compound to a constituent of some other is viewed with less excitement as we gradually become more acquainted with the intricacies of metabolic pools. It has, however, become more important than ever to determine the quantitative significance of one reaction with respect to the sum total of metabolic pathways.

A metabolizing system usually presents so many variables that a mathematical description is either impossible or only crudely approximate. By preserving the more important features of such a system, while neglecting some of its details, it is sometimes possible to find a useful approximation through the use of differential or integral equations. The main difficulty with such a presentation has been to keep it in a form which is both simple enough to be useful to the research worker, yet complete enough to avoid gross inaccuracies. It is the purpose of this paper to discuss the application of simple isotope kinetics to the calculation of turnover rates in metabolic systems.

DEFINITION OF CONCEPTS

Specific Activity. The specific activity (S) of a substance containing a labeled atom is the amount of radioactivity per unit of substance. One can express the specific activity of substance "A" (S_A) as the number of radioactive units (microcuries, counts per minute) per milligram or millimol of "A." A different expression is also in common use, namely, the percentage of the administered radioactivity per milligram or millimol of labeled "A." This latter quantity is commonly used to compare two animals that have received different quantities of radioactivity.

Steady State. In a normal adult the concentration of blood and tissue components is held at nearly constant concentrations while new synthesis and breakdown of chemical constituents proceeds. In a situation in which the rate

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of entry of a molecule "A" by synthesis or transport equals the rate of exit by breakdown or transport, the concentration of "A" remains constant and a steady state is said to exist. An increase in the concentration of "A" may result not only from an increase in the rate of "A" formation but also from a decrease in "A" loss, or both.

A non-steady state exists whenever the influx of material does not balance the outflux. A growing person is, strictly speaking, not in a steady state although in most instances the rate of growth is so small compared to the rate of metabolism that the condition may be treated as a steady state system. A person in negative nitrogen balance is not in a steady state with regard to his environment, but a particular compartment within the body (brain protein) might still be in a steady state. Whether or not the dynamics of the steady state are applicable in a certain condition depends, then, on the relative magnitudes of the imbalance of the rates of in- and outflux.

Turnover. This term refers to the process of renewal of a substance "A" in the body or in a given tissue. Renewal may take place in two different ways: (1) a substance "B" may be synthesized in a given tissue or (2) substance "B" may be synthesized somewhere else and arrive in the tissue cells by means of the bloodstream.

Turnover Rate. The rate at which a substance is turning over in a given compartment or metabolic pool (amount per unit of time). The meaning of turnover rate is unequivocal only when a steady state exists, i.e., when the rate of synthesis and transport into a compartment equals the rate of breakdown and exit.

Fractional Turnover Rate. The fraction or percentage of a compartment that is turning over or renewed per unit of time.

Turnover Time. The turnover time of a substance is the time that is required for the turnover of a quantity of substance equal to that present in the compartment. It should be understood clearly that during the turnover time not all the "old" molecules are replaced by "new" ones. It will be shown in a subsequent section that during that interval only 63 per cent of the "old" molecules have been replaced by "new" ones, if the tissue in question does not preferentially metabolize either "kind" of molecule. Turnover time is also a measure of the average lifetime of a molecule of the substance under consideration.

TURNOVER VERSUS NET SYNTHESIS AND EXCHANGE

A great deal of confusion has accompanied the use of the term "turnover." This is true in the case in which turnover consists of the construction of new molecules from smaller fragments and their subsequent breakdown, as well as when transport of a molecule from one organ to another is involved. Frequently the problem appears to be semantic, resulting from the failure of the writer to specify the type of turnover he is trying to measure. We have already discussed the limitations of the term "turnover" to a condition in which a steady state is maintained. Such usage would then preclude application of the term turnover to systems in which "net synthesis" occurs.

If someone asks what the turnover rate of blood glucose is, the question cannot be answered without further inquiry into the interests of the speaker. In its broadest sense the turnover of blood glucose includes several rates. First of all the total rate of entry of glucose into the circulation and the rate of its removal constitutes turnover; this is the kind of turnover that the physiologist might investigate. Secondly, the transfer of glucose between blood plasma and the formed elements of blood constitutes a type of turnover of particular interest to the cellular biologist. The physiologist whose interest was primarily in the rate at which glucose entered and left the circulation might consider the plasma and blood cells as one compartment and designate the transfer of glucose between cells and plasma as "merely exchange." He might ignore the fact that the "physiological turnover" of blood glucose includes the rate of "exchange" of glucose across capillary membranes unless the physiologist wishes to consider all extracellular fluid as one compartment and determine only the transfer of glucose between organs and extracellular fluid. In that case he is really measuring the glucose turnover rate in the extracellular fluid compartment and not in blood. Finally, the biochemist might say that the turnover rate of glucose in blood is zero since, according to his usage of the word, turnover exists only when molecules are being built up and degraded. Obviously, therefore, the frame of reference of the speaker or writer must be defined before the term "turnover" can acquire a precise meaning.

There is another difficulty encountered in the use of the term turnover or turnover rate when

these terms are applied to molecules, the components of which turn over at different rates. Let us consider, for example, the turnover of serum lipoproteins. These molecules consist of many units: cholesterol, lecithin, triglyceride, amino acids and others. Does such a molecule have a unique turnover rate? It is known from *in vitro* studies that cholesterol and phospholipids readily "exchange" between different lipoprotein molecules. These exchange rates may or may not be the same. It is possible that in the presence of certain enzymes the amino acids of a lipoprotein molecule might switch in and out of the chain. Depending upon the point of view of the investigator each one of these "exchange rates" may be of interest and would constitute a type of turnover of the lipoprotein molecules. Unfortunately one can no longer assign a unique turnover rate to the lipoprotein molecules as a whole. There is, however, still a meaning of lipoprotein turnover which could, at least in principle, be uniquely designated. Suppose, for example, that an investigator were interested in measuring the rate of transcapillary transfer of lipoproteins, if such a process exists. He would wish to determine the rate at which lipoprotein molecules cross capillaries irrespective of the switching in and out of lipids or amino acids. For this investigator the switching in and out reactions would be "merely exchange" and they would only make it more difficult to determine the "true turnover rate."

The question of what constitutes turnover and what is "exchange" resolves itself into stating as clearly as possible the rates in which one is interested. If an investigator interested in transcapillary movement of lipoprotein measures with C^{14}-cholesterol a rate including exchange he would make an error in interpretation. If, on the other hand, he were interested in the movements of cholesterol molecules between different lipoproteins he could justifiably call that rate the turnover rate of lipoprotein cholesterol.

MINIMUM VALUES OF TURNOVER RATES AS A MEASURE OF TURNOVER

In order to simplify our discussion, let us illustrate the calculation of "minimum values" by citing the early work on the turnover of phospholipids. After administration of radioactive phosphate a certain percentage of the isotope is recovered in the phospholipid fraction of an organ. The presence of radioactive phosphorus in phospholipid molecules some time after the administration of P^{32}-phosphate indicates that these molecules are newly synthesized with respect to their phosphorus component.

Although the values for the percentages of the injected P^{32} incorporated into phospholipids have been used to compare the rates of phospholipid synthesis in different organs, such values do not afford an adequate measure of the actual amounts of phospholipid formed. If, for example, 10 per cent of the P^{32}-phosphate administered is found in the phospholipid fraction of an organ, this means that 10 per cent of the phosphate administered was converted to phospholipid in that organ. This expression acquires meaning when we wish to learn the fate of exogenous phosphate; however, as an index of phospholipid synthesis, it will give erroneous results in most cases. We can perhaps best illustrate this with a numerical example. Let us assume that we have administered 1 μc. of P^{32} contained in 10 mg. of phosphate and that after six hours we find 1 per cent of the injected P^{32} in the phospholipid of the liver. This means that in the time interval indicated $\frac{1}{100} \times 10$ mg. or 0.1 mg. of the phosphate administered was converted to liver phospholipid. However, it does not mean that during these six hours only 0.1 mg. of the body's phosphate was converted to liver phospholipid. If the amount of phosphate in the body which is in rapid equilibrium with the injected phosphate were estimated to be 1 gm., then at least $\frac{1}{100} \times 1$ gm. or 10 mg. of body phosphate was converted to liver phospholipid in the six-hour interval.

As far as the total conversion of phosphate to phospholipid is concerned, a significant answer can be obtained only when the size of the phosphate pool is known or when the amount of phosphate administered is large when compared to the body phosphate readily exchangeable with the injected dose. In this case, however, the animal is flooded with unphysiological amounts of phosphate and the answer may be worthless as an indication of normal metabolism.

These considerations lead to the following conclusions: The percentage of the administered radioactive phosphate recovered in the phospholipid fraction is an accurate index of the amount of phosphate administered and converted to phospholipid, but provides only a minimum value for the amount of phospholipid synthesized in the body, a minimum value which may be far below the true rate of phos-

pholipid synthesis. A closer approximation may be obtained when information concerning the immediate precursor is available.

THE CONCEPT OF IMMEDIATE PRECURSOR AND SOME CONSIDERATIONS CONCERNING THE RATE DETERMINING STEP

The term precursor refers to a compound A which gives rise to B by chemical transformation or by transport from one organ to another. In the dog, plasma phosphate is a precursor of liver lecithin (chemical transformation) and liver lecithin is a precursor of plasma lecithin (transport).

In order to designate A a precursor of B, all that has to be known is that somehow, possibly through many intermediate reactions, A can become part of B. In this sense one speaks of acetate as a precursor of plasma cholesterol since it is known that C^{14}-acetate eventually becomes incorporated into a plasma cholesterol molecule. For the quantitative evaluation of turnover rates it is very useful to know which compound A immediately precedes the formation of B. Such a precursor we designate as the immediate precursor of B.

It must at once be obvious that it is not easy to detect the immediate precursor of a compound in a biological system containing dynamic equilibrium mixtures of all types of molecules at different energy levels. The immediate precursor may be some radical which exists only for a fleeting moment at the top of an "energy hill" or it may be present in such small amounts that not even the most sensitive chemical tests could detect it. In such a case the calculation of turnover rates requires only knowledge of the immediate specific activity of the precursor rather than its identification. It is fortunate that when the real immediate precursor is so evasive there usually exists some other substance which has, from moment to moment, the same specific activity as that of the precursor. Our next task, then, should be to determine under what conditions the specific activity of some compound, other than the immediate precursor, can be used for the calculation of turnover rates.

Let us suppose that exchange of phosphate between the plasma inorganic phosphate pool and that of the immediate precursor of liver lecithin were instantaneous; then a calculation of the rate of lecithin turnover could be based on the measurement of the specific activity of plasma inorganic phosphate. Even if the formation of liver lecithin from some phosphorus-containing intermediate were the rate-determining step in the reaction chain, and if this intermediate equilibrated with plasma phosphate rapidly (fast compared to the rate determining step), a phospholipid turnover rate based on the specific activity of plasma phosphate would still be accurate. If, however, the conversion of plasma phosphate to the precursor and the conversion of the latter to lecithin, were two slow reactions, then information about the specific activity of the immediate precursor at the site of reaction would generally be required. However, even in this case the possibility exists that the immediate precursor is present in an amount small in comparison to that turned over per unit of time. For example, if the intermediate is present to the extent of 1 mg. and is turning over at the rate of 100 mg. per minute, its specific activity is at every instance practically identical with that of plasma phosphate.

In one of the following sections we shall describe a method for the detection of an immediate precursor from specific activity data. We should keep in mind, however, that any compound which conforms to the criteria set up for an immediate precursor may either be the immediate precursor itself or a compound having the same specific activity as the immediate precursor.

DEFINITIONS OF SYMBOLS AND CONDITIONS

In subsequent sections the following set of symbols will be used:

A and B represent the total amounts of precursor and product, respectively, present in a given compartment or metabolic pool. The letters A and B will sometimes also be used to refer to the compartment in question.

A* and B* indicate the total amounts of radioactive precursor and product, respectively, present in a given compartment or metabolic pool. Thus $\frac{A^*}{A}$ and $\frac{B^*}{B}$ denote the specific activities of precursor and product

$$\left(\frac{A^*}{A} = S_A, \frac{B^*}{B} = S_B\right).$$

p and q represent the respective turnover rates of precursor and product. Since our discussion is limited to steady state systems, the turnover rate refers to the total flux of material through the

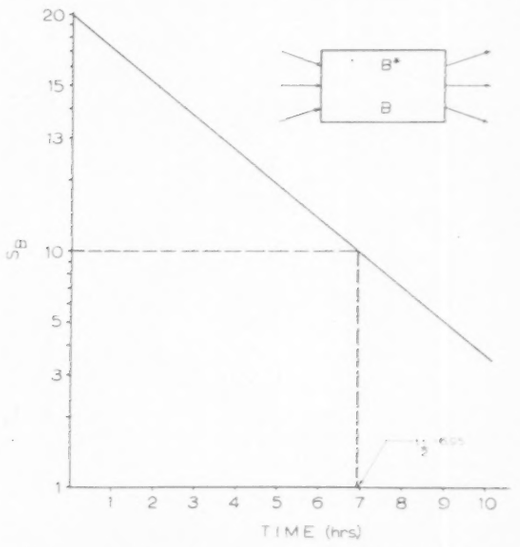


FIG. 1. Upper right: Blood constituent B is labeled with a single dose of B*. New B is delivered to the blood from three sources and disappears from the blood by three paths.

The graph shows the decrease in specific activity (S_B) of B plotted semi-logarithmically against time. The half-time ($t_{1/2}$) is the time in which the specific activity of B is halved (for example from twenty to ten hours) and is here equal to 6.95 hours.

compartment per unit of time (gm./hr., M/day, etc.).

k denotes the fraction of a compartment turned over per unit of time (fractional turnover rate, $k_1 = \frac{p}{A}$ and $k_2 = \frac{q}{B}$). The units of k are 1/time. Some investigators have called k the turnover rate [*1,2*] but this usage is not generally accepted and should be discouraged [*3*].

t_t, the turnover time, is the time required for the turnover of a quantity equal to the amount present in a given compartment. Thus for compartment A, $t_t = \frac{A}{p} = \frac{1}{k_1}$.

Unless otherwise stated we shall limit our discussion in this article to metabolic systems in which the following conditions hold: (1) The system is open, i.e., the isotope is continuously lost from the system by dilution with unlabeled exogenous material and by subsequent excretion. (2) A steady state exists, the total rate of inflow of a product B (synthesis, transport, etc.) equals the rate of outflow (breakdown, transport). This rate, the turnover rate of B, equals q. (3) The turnover rates of precursor and product remain constant (but not necessarily equal) during the period of the experiment (p and q are constant). (4) Random breakdown prevails, i.e., the organism does not distinguish radioactive and non-radioactive molecules, nor does it differentiate between newly synthesized and old molecules. The metabolic breakdown and transport of old and new molecules, of radioactive and non-radioactive molecules occur in proportion to their tissue concentrations. In the red cell this condition does not hold since older cells are known to disappear from the circulation before young cells [*4*].

In subsequent illustrations examples were selected to indicate a method of approach. The numerical solutions may serve as models ready for use by future investigators. The selection in no way implies that these models are of greater importance than those described elsewhere in the literature [*5–10*]. Hydrodynamic and electrical models have also been proposed [*11–15*].

DISAPPEARANCE OF INTRAVENOUSLY ADMINISTERED LABELED PRODUCT

Perhaps the simplest model for the calculation of turnover rate is the case in which a substance like glucose (B) is present in blood plasma and is administered in the labeled form, B*, by the administration of a single intravenous injection. If the weight of labeled glucose administered is small compared to the total glucose present in the circulation we speak of a "tracer dose" of glucose. The total rate of turnover (q) may consist of several components (Fig. 1); B may be contributed by liver, intestine and muscle whereas it is removed by kidney, lung and pancreas. For simplicity we shall consider the case in which labeled B (B*) does not return to the blood from the tissues. Although in the glucose experiment the total amount of glucose in the blood is constant from one time to the next, the isotopically labeled glucose is constantly removed from the circulation and replaced by the same weight of non-labeled glucose. Consequently, the specific activity of the plasma glucose decreases continually and the rate of decrease at a given time (t) depends upon the size of the blood glucose compartment (B), the rate of blood glucose turnover (q), and the amount of labeled glucose present at the time in question (B*). Mathematically one may represent this relation as $\frac{dS_B}{dt} = -\frac{qS_B}{B}$ in which S_B is the specific activity of B. In words this equa-

tion reads as follows: the change of specific activity per infinitesimal unit of time is equal to the rate of glucose turnover, times the specific activity of glucose, divided by the size of the glucose pool. The minus sign indicates that the specific activity decreases. If we substitute k_2 for q/B we obtain

$$\frac{dS_B}{dt} = -k_2 S_B \qquad (1)$$

or its integrated form

$$S_B = S_B^0 e^{-k_2 t} \qquad (2)$$

in which S_B^0 is the specific activity of B at zero time. The numerical value of S^0 can ordinarily be obtained by plotting log S against time and extrapolation of the line to zero time; k_2 may be obtained from the slope. More convenient is the use of semi-log paper. (Fig. 1.) One may obtain S_B^0 again by extrapolation and the fractional turnover rate k_2 directly from the relation

$$\frac{1}{k_2} = t_t = 1.44\ t_{1/2}.* \qquad (3)$$

From Figure 1, $t_{1/2} = 6.95$ hour and $k_2 = \frac{1}{1.44 \times 6.95} = 0.10$ per hour; i.e., 1/10 of B is turned over per hour and the turnover time is ten hours. To obtain the turnover rate q we must know the size of compartment B.

The determination of compartment size is closely related to the determination of plasma volume by a dilution principle. If an injected dye distributes itself only in the plasma compartment and is not metabolized or excreted, the volume is obtained simply by dividing the plasma concentration of the dye into the injected dose. If the dye is metabolized, secreted or sequestered slowly the procedure is supplemented by taking several samples and extrapolating their concentration to zero time.

To determine the size of the glucose compartment in the previous example the proceedings are as follows: An injection of 100 μc. of radioactive glucose (B*) might be used and the disappearance curve determined as in Figure 1. The units on the ordinate are specific activities, and the zero time (extrapolated) specific activity (S_B^0) is 20 μc. per gm. of glucose. This means that the injected glucose equilibrated rapidly with a glucose pool (B) of $\frac{100}{20}$ or 5 gm. This pool might represent a physiological compartment such as the extracellular glucose, but it might also include some of the intracellular glucose which is in rapid exchange equilibrium with extracellular glucose. Although the total size of the pool in grams can be determined in this way, it is not always possible to identify the spatial distribution of the substance in question.

Now that the fractional turnover rate (k = 0.1 per hour) is known and a pool size of 5 gm. has been determined, it is a simple step to obtain the turnover rate q: q = kB = 0.5 gm. per hour. This means that the total flux of glucose in and out of the "extracellular" glucose pool is 0.5 gm. per hour.

At this point the dynamic equilibrium pictured in Figure 1 should be reconsidered. A 5 gm. pool of glucose is replenished with new molecules at the rate of 0.5 gm. per hour and simultaneously depleted at the same rate. If in this system a tracer dose of radioactive glucose is injected, the radioactive molecules will disappear in proportion to the number of radioactive molecules left at any one time. For a given 100 molecules approximately one-tenth, or 10, will disappear the first hour. Of the remaining 90 again one-tenth, or 9 will vanish the next hour. This will occur hour after hour. Although the percentage of radioactivity disappearing during an hour is always the same, the absolute amount leaving per hour decreases as the total amount of radioactive glucose in the circulation decreases. In one half life 50 per cent of the radioglucose has left the circulation. In another half life an additional 25 per cent of the original dose injected will be gone, and in yet another half life 12.5 per cent more has left. This exponential decrease or "die-away" curve occurs not only in the biological system just described but also in other forms of dilutions, in radioactive decay, and in the loss of heat from the surface of a hot object immersed in an environment of constant temperature.

In the foregoing paragraphs we have presented the reasoning and methodology in detail since a thorough grasp of this simple situation

* From equation 2, $k_2 t = \ln \frac{S_B^0}{S_B}$. At $t = t_{1/2}$, $k_2 t_{1/2} = \ln 2 = 0.693$ and $\frac{1}{k_2} = 1.44\ t$. This equation is useful also for specific activity-time curves of more than one component. For each component $\frac{1}{k}$ is then equal to 1.44 times the corresponding half time.

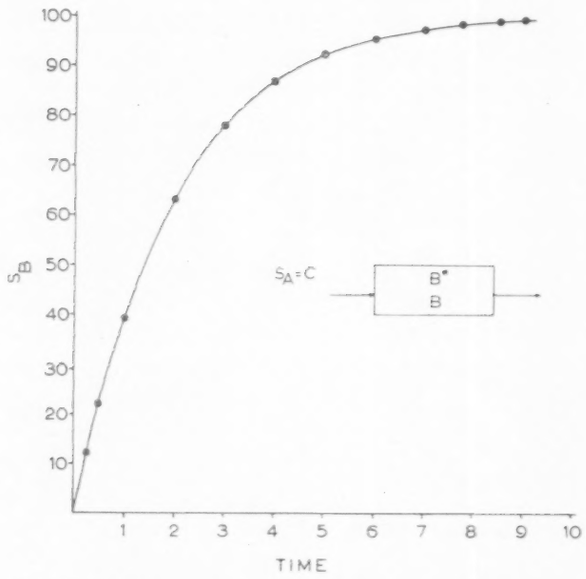


FIG. 2. Specific activity of B (S_B) versus time in days. The specific activity of the precursor is constant.

will greatly facilitate the approach to more difficult problems.

THE SPECIFIC ACTIVITY OF THE PRECURSOR IS CONSTANT

A second model which was used much in the early days of isotope experimentation but which seems to have been neglected recently is the one in which the specific activity of a precursor is kept constant ($S_A = c$). The daily feeding of D_2O is a classic example of this technic [*16*]. The change in the total amount of isotope in compartment B, $\frac{dB^*}{dt}$, is governed by the rate of entry of isotope, qc, and the rate of exit, qS_B. (See Figure 2 in which only one way transport is considered.)

Thus

$$\frac{dB^*}{dt} = q(c - S_B) \qquad (4)$$

and dividing by B on both sides while substituting k for q/B,

$$\frac{dS_B}{dt} = k_2(c - S_B) \qquad (5)$$

which upon integration gives

$$S_B = c(1 - e^{-k_2 t}) \qquad (6)$$

Figure 2 shows an example for $k_2 = 0.50$. The specific activity of B approaches an upper limit

TABLE 1
FRACTIONAL TURNOVER RATES FOR DIFFERENT VALUES OF S_B/S_A WHEN S_A IS CONSTANT (LEFT) OR WHEN IT INCREASES LINEARLY WITH TIME (RIGHT)

$S_A = c$; $S_B/S_A = (1 - e^{-k_2 t})$				$S_A = bt$; $S_B/S_A = \frac{1}{k_2 t}(k_2 t - 1 + e^{-k_2 t})$			
S_B/S_A	$k_2 t$	S_B/S_A	$k_2 t$	S_B/S_A	$k_2 t$	S_B/S_A	$k_2 t$
.050	.051	.525	.74	.050	.10	.425	1.23
.075	.078	.550	.80	.075	.16	.450	1.34
.100	.11	.575	.86	.100	.21	.475	1.47
.125	.13	.600	.92	.125	.27	.500	1.59
.150	.16	.625	.98	.150	.33	.525	1.74
.175	.19	.650	1.05	.175	.40	.550	1.89
.200	.22	.675	1.12	.200	.47	.575	2.05
.225	.25	.700	1.20	.225	.53	.600	2.23
.250	.29	.725	1.29	.250	.61	.625	2.42
.275	.32	.750	1.39	.275	.68	.650	2.65
.300	.36	.775	1.49	.300	.76	.675	2.91
.325	.39	.800	1.61	.325	.85	.700	3.20
.350	.43	.825	1.74	.350	.93	.725	3.53
.375	.47	.850	1.90	.375	1.03	.750	3.92
.400	.51	.875	2.08	.400	1.13	...	...
.425	.55	.900	2.30	...	...	...	...
.450	.60	.925	2.59	...	...	...	...
.475	.64	.950	2.99	...	...	...	...
.500	.69	.975	3.69	...	...	...	...

which equals the specific activity of the precursor. To determine k_2 in any given experiment it is sufficient to obtain the ratio of the specific activity of B at some early time interval to that of the precursor, S_B/S_A (see left side of Table 1). For example, in the experiment in Figure 2 the specific activity of the precursor is 100 μc./gm. In one day the specific activity of B equaled 39 μc./gm. Table 1 shows that for a specific activity ratio of $S_B/S_A = 0.39$, $k_2 t = 0.50$ and since $t = 1$ day, $k_2 = 0.50$ per day, and the turnover time equals two days. It is noteworthy that in this case after two days, or in general after one turnover time ($k_2 t = 1$, Table 1), the specific activity ratio of product to precursor equals 0.63. This means that although an amount of new material equal to that present in the compartment has flowed through, only 63 per cent of the molecules are "new" molecules (synthesized since the beginning of the experiment), whereas 37 per cent of the molecules present before introduction of the isotope are still there. This also means that by the time one turnover time has elapsed 37 per cent

of the newly synthesized molecules already have disappeared.

In the previous discussion it has been assumed that the specific activity of the precursor was held constant and that only one precursor was present. However, a situation is frequently encountered in which the latter restriction is not valid and several precursors exist. Consider, for example, the metabolism of serum cholesterol. There are probably a number of tissues that contribute endogenous cholesterol to the blood plasma and in addition the diet constantly furnishes cholesterol from exogenous sources. If, for the moment, the problem of the possible inhomogeneity of plasma cholesterol is ignored and all of plasma cholesterol is treated as one pool, the sources of plasma cholesterol could be divided into two portions: one of the precursors, i.e., dietary cholesterol, could be labeled with C^{14} and the others (acetyl coenzyme A, etc.) left unlabeled.

To draw an idealized example, let a plasma cholesterol compartment B with an influx of p gram per day from a precursor with a specific activity equal to c, and r gram from an unlabeled source (endogenous synthesis) be assumed. The total turnover rate of pool B is q, which is p + r. The change in B^* per unit of time, $\frac{dB^*}{dt}$, is determined by the rate of influx of label pc and its rate of exit,

$$q\,\frac{B^*}{B},\ \text{i.e.,}\ \frac{dB^*}{dt} = pc - qS_B \qquad (7)$$

This equation can be transformed to the same form as equation 5 by the following considerations: the specific activity of B will approach an upper limit $S_{B_{max}}$ which in this case does not equal that of the precursor but is determined by the fraction of B derived from each source, $\frac{p}{q}$ and $\frac{r}{q}$. In consequence $S_{B_{max}} = \frac{p}{q}c$. The substitution $c = S_{B_{max}}\frac{q}{p}$ is made and both sides of equation 7 are divided by B; thus

$$\frac{dS_B}{dt} = k_2(S_{B_{max}} - S_B) \qquad (8)$$

is obtained in which $k_2 = \frac{q}{B}$. This equation is entirely analogous to equation 5 and has the same solution except that $S_{B_{max}}$ takes the place of c;

$$S_B = S_{B_{max}}(1 - e^{-k_2 t}) \qquad (9)$$

and again we may determine k_2 from Table 1 when $S_B/S_{B_{max}}$ is known at a single early time interval.

The analogy between this case and the case in which only one precursor is present should not blind us to the fact that the experimental design in the two cases differs considerably. To obtain k_2 when only one precursor is present it is sufficient, in theory at least, to take one sample of plasma (B) at a relatively early time interval, determine its specific activity, and divide that by the known specific activity of the precursor (c). In the second instance the specific activity of B must be divided by $S_{B_{max}}$, and $S_{B_{max}}$ is not known unless the experiment is continued until the time of equilibration. If an animal were sacrificed and other tissue samples taken prior to the time at which the plasma specific activity reaches a plateau, how could the k_2 for plasma cholesterol be determined? The solution is a relatively simple one. If we determine the specific activity of plasma cholesterol, S_B at two time intervals before equilibration (t_1 and t_2) the ratio

$$R = \frac{(S_B)_{t_1}}{(S_B)_{t_2}} = \frac{1 - e^{-k_2 t_1}}{1 - e^{-k_2 t_2}} \qquad (10)$$

no longer contains $S_{B_{max}}$.

The calculation of k_2 from equation 10 is somewhat difficult. Therefore, Figure 3 has been so constructed as to allow its determination for six different ratios of $\frac{t_1}{t_2}$.* As a hypothetical example, consider the case in which the first sample is taken two days and the second sample ten days after the beginning of the experiment ($t_1 = 2$, $t_2 = 10$) should be considered. The specific activity of B was 3 μc./mg. at the first time interval and 10 μc./mg. at the second, so that R = 0.3. Using the fifth curve ($t_1/t_2 = 0.20$) we find that $k_2 t_1 = 0.225$, thus $k_2 = \frac{0.225}{2} = 0.112$ per day. The turnover time of plasma cholesterol is then $\frac{1}{k_2} = \frac{1}{0.112} = 8.9$ days.

The value of k_2 so obtained is useful not only for its own sake but also to calculate what the final plasma specific activity would have been

* The ordinate of Figure 3 shows k.t instead of $k_2 t$. In this example $k = k_2$. In equation 15, $k = (k_2 - k_1)$.

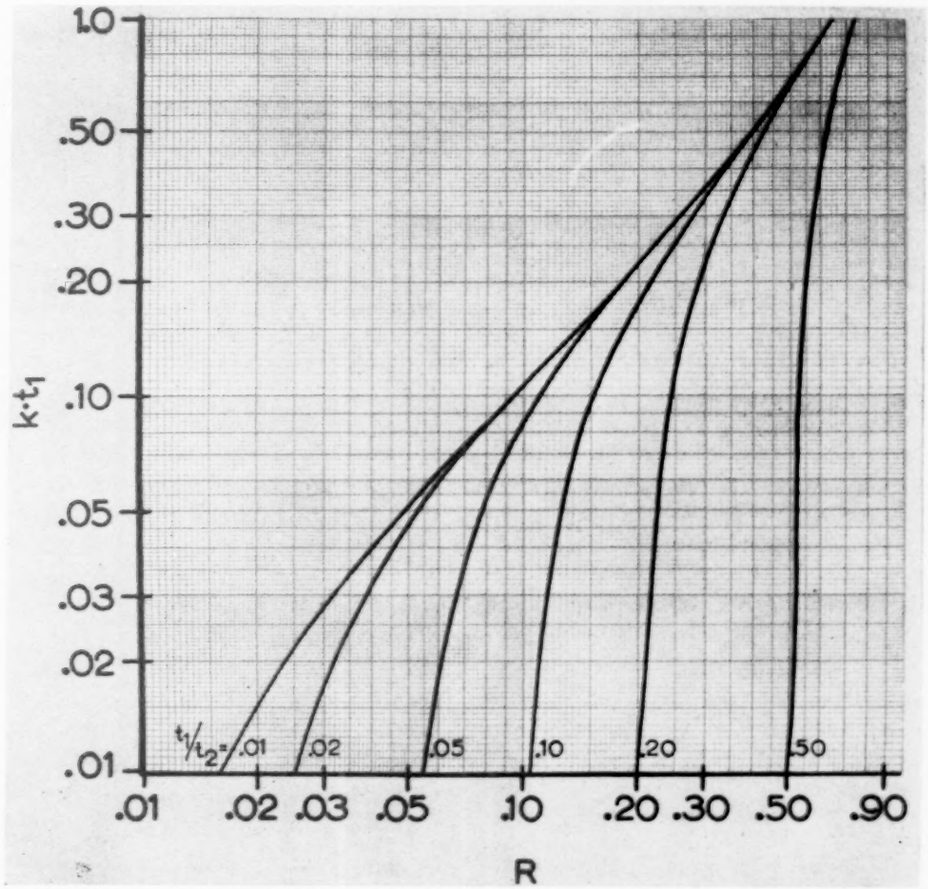


FIG. 3. Log-log plot of the product of fractional turnover rate and time (kt_1) against the ratio of specific activities at two different time intervals $\frac{(S_B)_{t_1}}{(S_B)_{t_2}} = R$. Six curves are drawn for different values of t_1/t_2.

had we carried out the experiment for "infinite" time.

From $S_B = S_{B_{max}}(1 - e^{-k_2 t})$,

or $3 = S_{B_{max}}(1 - e^{-.225})$,

we find $S_{B_{max}} = 15\ \mu c./mg.$

If the specific activity of the constantly labeled dietary cholesterol was 20 $\mu c./mg.$, then the fraction of the plasma cholesterol turnover derived from that source

$$p/q = S_{B_{max}}/c = {}^{15}\!/_{20} = 0.75$$

If 75 per cent of plasma cholesterol turnover derives from the diet, 25 per cent must come from endogenous sources. By an interpretation somewhat similar to this one Morris et al. concluded that rats on a high cholesterol diet have relatively less endogenous cholesterol in their blood plasma than animals kept on a low cholesterol intake [*17*]. Unfortunately, no early specific activity data are given so that turnover rates could not be determined.

The average specific activity of serum cholesterol between the beginning of the experiment and the time of termination ($t_2 = 10$) may be found as follows:

$$S_{B_{av}} = \frac{S_{B_{max}}}{t_2 - t_1} \int_{t_1}^{t_2} (1 - e^{-k_2 t})\, dt$$

$$S_{B_{av}} = \frac{15}{10 - 0} \int_{0}^{10} (1 - e^{-0.112t})\, dt$$

which is equal to 6 $\mu c./mg.$ This average specific activity may be used in turn to make an estimate of how much serum cholesterol was transported to a given tissue. With an average specific activity for serum cholesterol of 6 $\mu c./mg.$, and ignoring the fact that some of the radioactive cholesterol in the tissue may have been catabolized or transported away before

sacrificing the animals, we may estimate that for every microcurie of cholesterol found in a given tissue at least 1/6 mg. of serum cholesterol was transported to that tissue in the ten-day interval. It is obvious that such an estimate is valid only relatively early in an experiment when the tissue breakdown of cholesterol can indeed be ignored without great error. Apparently the continuous administration of a precursor of constant specific activity allows the calculation of blood and tissue turnover rates by relatively simple technics. It is important, however, to perform preliminary experiments justifying the assumptions made in the calculations cited.

THE SPECIFIC ACTIVITY OF THE PRECURSOR INCREASES LINEARLY WITH TIME

The case in which the specific activity of the precursor increases steadily is not as common as that in which the specific activity is held constant, but is approximated when a single dose of radioactive isotope is administered at a site from which the isotope is only slowly absorbed. One also sees an approximately linear increase in the specific activity of the precursor if the isotope is administered to the animal in a form which must first be converted to the precursor in question. For example, after the administration of a single intravenous injection of radioactive phosphate in a dog, we found that for at least fifteen hours the specific activity of liver sphingomyelin increased linearly [*18*]. Knowing that liver sphingomyelin is the immediate precursor of plasma sphingomyelin, the rate of sphingomyelin transport from liver to plasma may be calculated if the investigator assumes little or no return of plasma sphingomyelin to the liver. If compartment A represents liver sphingomyelin and B the sphingomyelin of plasma, and during the early part of the experiment the specific activity of liver sphingomyelin is proportional to time ($S_A = bt$), then the differential equation is similar to equation 5 in which bt is substituted for c. After integration we obtain

$$S_B = \frac{b}{k_2}(k_2t - 1 - e^{-k_2t}) \text{ where } k_2 = \frac{q}{B}$$

Since, as stated previously, $S_A = bt$, this equation may be written in the form of a relative specific activity:

$$\left(\frac{S_B}{S_A}\right)_t = \frac{1}{k_2t}(k_2t - 1 - e^{-k_2t}) \qquad (11)$$

The values of k_2t for different values of S_B/S_A are given. (See right side of Table 1.) In experiments with animals (in dog No. 44 [*18*]) in which the specific activity of the precursor increased linearly with time, we observed a ratio of the specific activity of plasma sphingomyelin to that of liver sphingomyelin of 0.45, fifteen hours after injection of P^{32}-phosphate. Thus from Table 1 $k_2t = 1.34$ and $k_2 = 1.34/15 = 0.089$ per hour, or a turnover time of plasma sphingomyelin of eleven hours. This value was in good agreement with a turnover time of twelve hours obtained from the intravenous injection of P^{32}-labeled sphingomyelin and calculated by equation 3 [*19*].

THE SPECIFIC ACTIVITY OF THE PRECURSOR DECREASES EXPONENTIALLY WITH TIME

When a single dose of labeled material is introduced into compartment A (plasma) and disappears from the plasma exponentially, as illustrated in Figure 1, it is conceivable that this substance serves as a precursor for a second substance, B. If none of B is assumed to return to A we may write, in an analogy with equation 2,

$$S_A = S_A^0 e^{-k_1t} \qquad (12)$$

where S_A^0 is the specific activity of A at zero time and $k_1 = \frac{p}{A}$. The differential equation is again analogous to equation 5, with S_A substituted for c. If $k_2 = \frac{q}{B}$ we obtain after integration

$$S_B = \frac{k_2}{k_2 - k_1} S_A^0 (e^{-k_1t} - e^{-k_2t}) \qquad (13)$$

This equation, graphically presented in Figure 4, contains three unknowns: S_A^0, k_1 and k_2. In a large animal or a patient the specific activity-time curve in plasma may be readily available and thus furnish S_A^0 and k_1 directly. Then only one sample from compartment B will suffice to calculate k_2. If the investigator is working with rats or mice in which it may not be practical to take serial blood samples, the following two paths are then open to him: (1) he may sacrifice a few animals at different time intervals and obtain a composite specific activity-time curve or (2) he may have two groups of animals and

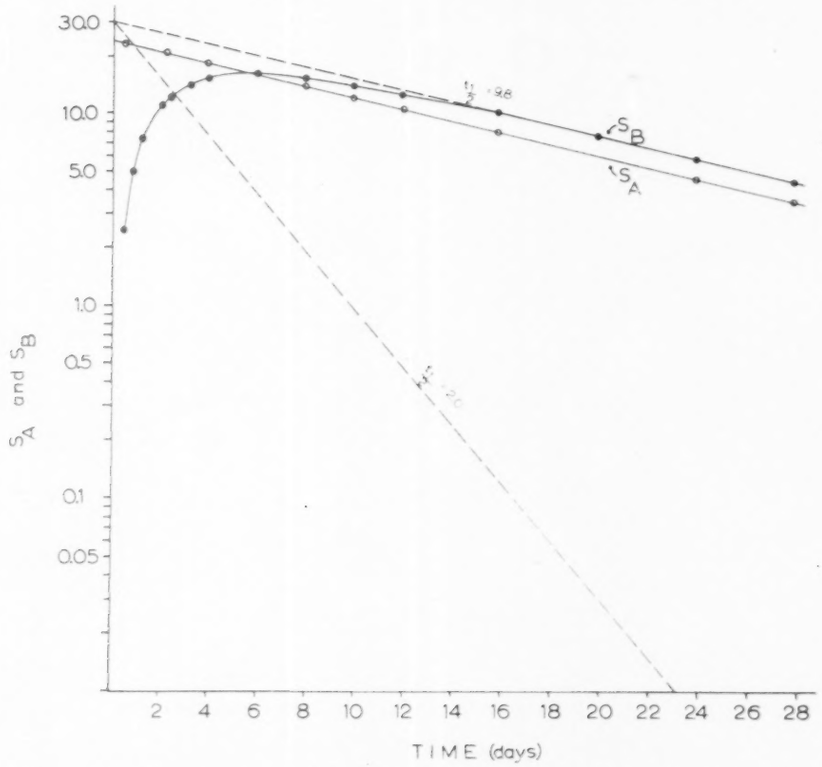


FIG. 4. Semi-log plot of specific activity of precursor (S_A = ○) and product (S_B = ●) when S_A decreases exponentially with time. The curve for S_B may be decomposed into two components by extrapolation of the final portion to zero time (upper dashed line) and subtracting the numerical values for the early portion of the S_B curve from the upper dashed line to give the lower dashed line.

sacrifice one group at time t_1 and the other at time t_2. A better alternative is to get samples of compartment A and B on each animal at two different times. The first alternative has the disadvantage that the variability from animal to animal makes it difficult to fit an exponential curve to experimental points exhibiting considerable scatter. The specific activity of a material such as liver phospholipid, for example, depends on the amount of P^{32} injected, the amount absorbed from the site of injection, the extent of dilution of P^{32} in various tissues, the rate of exchange with bone phosphate, the rate of precursor synthesis, as well as the actual rate of synthesis of the phospholipid. All of these factors are subject to individual variation. Since the immediate precursor of liver lecithin is affected by every factor to the same extent as the phospholipid itself (except, of course, the rate of phospholipid synthesis) the use of S_B/S_A eliminates all scattering influences except those exerted directly on the last biosynthetic step. Consequently, whenever it is possible to employ relative specific activities, such as S_B/S_A, to calculate individual turnover rates and then average these rates in many animals, the investigator is likely to arrive at more significant conclusions.

To calculate relative specific activities in the present instance, equation 13 may be rearranged by substitution of S_A for S_A^0 from equation 12 to give

$$\left(\frac{S_B}{S_A}\right)_t = \frac{k_2}{k_2 - k_1}\left[1 - e^{-(k_2 - k_1)t}\right] \qquad (14)$$

The ratio, R, of the relative specific activities at two time intervals, t_1 and t_2, equals

$$\frac{(S_B/S_A)_{t_1}}{(S_B/S_A)_{t_2}} = \frac{1 - e^{-(k_2 - k_1)t_1}}{1 - e^{-(k_2 - k_1)t_2}} \qquad (15)$$

and varies exactly as does R in Figure 3 with this difference that the ordinate now gives us $(k_2 - k_1)t_1$ instead of k_2t_1, as in equation 10. An illustration of the use of this equation may be

TABLE II
SPECIFIC ACTIVITIES OF PRECURSOR (S_A) AND PRODUCT (S_B) AT TWO AND TEN DAYS AFTER THE ADMINISTRATION OF ISOTOPE*

Time (days)	S_A	S_B	S_B/S_A
t_1 2	20.3	11	0.542
t_2 10	11.6	14	1.21

* Data obtained from Figure 4.

found in the data of Table II. (Taken from Fig. 4.) For these data the ratio $R = \frac{0.542}{1.21} = 0.45$. By the use of the curve labeled $t_1/t_2 = 0.2$ in Figure 3 we obtain for $R = 0.45$, $(k_2 - k_1)t_1 = 0.55$ and thus $k_2 - k_1 = \frac{0.55}{2} = 0.28$. Substituting this value in equation 14 for $t = 2$ gives $k_1 = 0.07$ per day and $k_2 = 0.35$ per day.

It should be emphasized that when the complete specific activity-time curves of A and B are available, as in Figure 4, the values for k_1 and k_2 are in general more accurately obtained by decomposing the complete S_B curve into two single exponentials (dashed lines). By equation 3, k_1 and k_2 were found to be 0.071 per day and 0.35 per day respectively, which agrees well with the 0.07 per day and 0.35 per day calculated in the previous paragraph from the data in Table II. Apparently, when the exponential nature of the precursor specific activity has been established, and one deals with a set of metabolic pools as described in the present example, accurate specific activities of A and B at two different times are sufficient to obtain reliable values for the fractional turnover rates of precursor and product.

Equation 13 also correctly predicts the time at which B reaches its maximum specific activity:*

$$t_{max} = \frac{1}{k_1 - k_2} \ln \frac{k_1}{k_2} \qquad (16)$$

For the data in Figure 4, t_{max} according to equation 16 is 5.7 days. Equation 16 holds in general except when k_1 and k_2 are equal. In this case equation 13 is transformed to $S_B = S_A^0 kte^{-kt}$ or $\left(\frac{S_B}{S_A}\right)_t = kt$ and equation 16 becomes $t_{max} = \frac{1}{k} = t_t$. Under these conditions k may be obtained from the $\frac{S_B}{S_A}$ at a single time interval. Or, when the time of maximum specific activity of B is known, $k = \frac{1}{t_{max}}$. Stated differently, in the case in which $k_1 = k_2$ the time at which the product reaches its maximal specific activity is equal to the turnover time. Even when k_1 and k_2 are not exactly equal the average turnover time of the precursor and product is close to t_{max}. This is illustrated by the data in Table III. When the turnover times of product and precursor are equal or less than 10 per cent apart the average of the two turnover times accurately predicts the time of the maximum specific activity of the product. Even when a 50 per cent difference between the turnover times obtains, the average is within a few per cent of the true maximum. When the differences are greater the simple average strikes farther from the true value. Although the approximate formula for the maximum has little to offer when precise specific activity time-curves are available, the location of the maximum when less

TABLE III
ESTIMATED AND CALCULATED VALUES OF TIME OF MAXIMAL SPECIFIC ACTIVITY*

Turnover Times			Time of Maximum Specific Activity by Equation 16
Precursor	Product	Average	
10.0	10.0	10.0	10.0
10.0	11.0	10.5	10.5
10.0	15.0	12.5	12.2
10.0	20.0	15.0	13.9
10.0	40.0	25.0	18.5

* The figures in the third column are the averages of the two turnover-times and serve to estimate the time of maximal specific activity of the product. They approximate the actual time of maximal specific activity (column 4). Inversely when it is known that the turnover-times of product and precursor are not too different the time at which the maximum specific activity occurs is a measure of the average of the two turnover-times.

* At $t = t_{max}$,

$$\frac{dS_B}{dt} = \frac{k_2}{k_2 - k_1} S_A^0 (k_2 e^{-k_2 t_{max}} - k_1 e^{-k_1 t_{max}}) = 0.$$

Consequently, $k_2 e^{-k_2 t_{max}} = k_1 e^{-k_1 t_{max}}$ or $\ln \frac{k_1}{k_2} = (k_1 - k_2)t_{max}$.

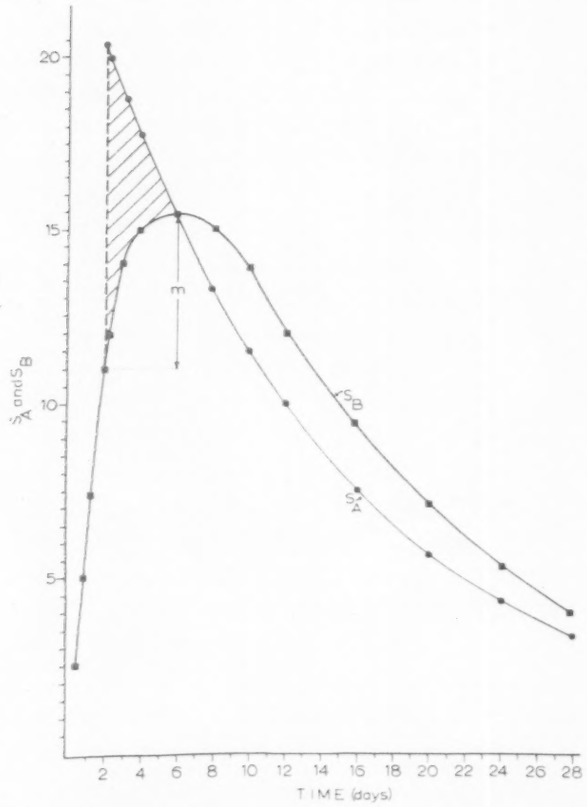


FIG. 5. Specific activities of precursor A (●) and product B (■) plotted against time. The data are the same as those in Figure 4; $t_1 = 2$ and $t_2 = 6$. The difference between the specific activities at these two times ($S_{B_{t_2}} - S_{B_{t_1}}$, equation 18) is equal to m. The difference between the areas under the S_A and S_B curves enclosed by ordinates erected at two and six days represents the difference between the integrals in equation 18 and is shown as a shaded area.

accurate data can be obtained may be of help in the estimation of approximate turnover times.

A practical example in which an exponential precursor function was used is the study of Baker et al. [*20*] on the oxidation of glucose in normal human subjects. C^{14}-labeled glucose was administered intravenously to normal subjects and the specific activity of plasma glucose determined at several time intervals. Simultaneously $C^{14}O_2$ was collected in the expired air. The authors assumed that, although the oxidation of glucose is a very complex process involving many intermediates, one could approximate the kinetic behavior of C^{14}-glucose by postulating the following two large metabolic pools: (1) the glucose pool, in rapid equilibrium with plasma glucose (A), and (2) the CO_2 pool, in rapid equilibrium with expired CO_2 (B). Equation 13 applies to this system except for one factor, namely, the additional CO_2 derived from non-labeled sources (protein, fat). This difference was, however, easily taken into account. To test the applicability of the proposed model the authors calculated k_1 from the disappearance of injected C^{14}-glucose and k_2 from the disappearance of injected $HC^{14}O_3^-$. In addition k_2 was calculated from k_1 at the time at which the CO_2 specific activity curve reached a maximum by equation 16. The two values for k_2 were 0.0097 and 0.0086 per minute, a good agreement for this type of measurement. The values for k_1 and the per cent of CO_2 derived from glucose were also subjected to verification by other means (see the original paper for details).

THE FUNCTION EXPRESSING THE SPECIFIC ACTIVITIES OF THE PRECURSOR IS NOT KNOWN

In many instances the algebraic expression for the specific activity of the precursor may not be known but a specific activity-time curve of precursor and product may be available. This allows determination of the fractional turnover rate by graphical means [*21*]. Figure 5 shows the specific activity-time relations of precursor A and product B. Although no use will be made of the exponential nature of the specific activity-time curves, the data in Figure 5 are the same as those used in Figure 4 but replotted on Cartesian graph paper. The specific activity of the precursor will here be designated f(t), indicating that it may be any function of time, and the specific activity of the product is designated S_B. The turnover rate of the product will be q, as before, and it is assumed that no B returns to compartment A. The change in B* per unit of time will then be expressed as $\frac{dB^*}{dt} = q[f(t) - S_B]$, and the change in specific activity as

$$\frac{dS_B}{dt} = k_2[f(t) - S_B] \qquad (17)$$

Some general properties of the precursor-product curves may be derived by inspection of equation 17 and Figure 5. When $\frac{dS_B}{dt} = 0$, i.e., when the specific activity of B has reached a maximum, $k_2[f(t) - S_B] = 0$ or $f(t) = S_B$. The specific activities of precursor and product are equal when the latter reaches its maximum value. Since prior to the time of maximum activity the

specific activity of the precursor exceeds that of the product, whereas beyond that time the reverse situation holds, it can be predicted that at the time of maximum specific activity of the product the two specific activity curves must cross. This property of precursor and product is so characteristic that in certain instances it may be used to eliminate a compound as the precursor of another; in other instances it may strengthen the evidence for a precursor-product relationship between two substances. Perhaps it should be emphasized that the crossing of the precursor-product specific activity curves takes place only under certain conditions. In metabolic systems in which there is more than one precursor or in which the product compartment is not homogeneous, the two curves will not cross. Furthermore, it should be stated that the crossing of two specific activity curves is not sufficient evidence for a precursor-product relation. In the case where precursor A is in rapid isotopic equilibrium with A′ which is chemically not a precursor of B we would still find the specific activity curves of A′ and B to cross. Within the type of restricted systems under discussion the crossing of specific activity curves is a necessary but not a sufficient condition for a precursor-product relationship.

Equation 17 may be integrated as follows:

$$S_{B_{t_2}} - S_{B_{t_1}} = k_2 \left[\int_{t_1}^{t_2} f(t)\, dt - \int_{t_1}^{t_2} S_B\, dt \right] \tag{18}$$

The difference at the left is equal to m and the quantity between square brackets is equal to the shaded area in Figure 5, so that we may conclude that

$$k_2 = \frac{m}{\text{shaded area}} \tag{19}$$

When applied to the data in Figure 5, k_2 is found to be 0.34, which is in excellent agreement with the value 0.35 obtained in the previous section. It is needless to say that the two times, t_1 and t_2, between which the hatched area is calculated may be chosen along any portion of the curves. In general one should select several different time intervals and obtain an identical value for k_2 as a check on the suitability of the assumed model. Although the method discussed in this section allows the calculation of turnover times without prior knowledge of the dependence of specific activities on time, it does require more extensive experimental data. Whereas with the methods previously discussed it was possible to determine turnover times from specific activity data at one or two time intervals, the present method requires a sufficient number of points to delineate at least a portion of the two specific activity-time curves.

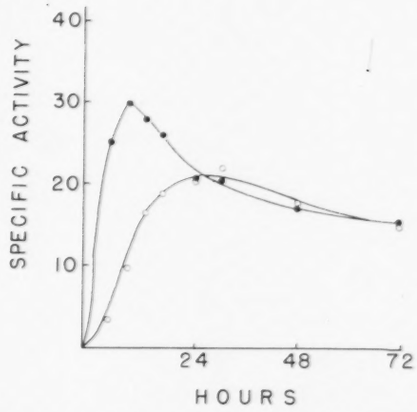


FIG. 6. Specific-activities of bile lecithin (●) and plasma lecithin (○) at various time intervals in a dog injected with a single dose of P^{32}-phosphate.

As an example of this method consider the turnover rate of plasma lecithin in the dog. In early experiments dogs were injected with P^{32}-phosphate whereupon plasma and liver biopsy specimens were obtained at various time intervals for lecithin analysis [*18*]. Since multiple liver biopsies were rather traumatic to the animal, later experiments were improved by collecting bile lecithin instead of the lecithin from liver [*22*]. The collection of bile lecithin had the further advantage that it probably more closely approximated the plasma lecithin precursor since liver apparently contains some lecithin that turns over more slowly than that poured into bile and plasma. A typical set of specific activity curves is reproduced in Figure 6. Application of equation 19 to four dogs gave a value for the turnover time of plasma lecithin of fourteen hours [*22*]. This compares favorably with an average turnover time of twelve hours obtained from the disappearance of intravenously administered P^{32}-lecithin-labeled phospholipoproteins and calculated by equation 3 [*19*].

MULTIPLE PRECURSORS AND INHOMOGENEITY OF THE METABOLIC POOLS

As indicated in previous sections the simple assumptions enumerated earlier may not always

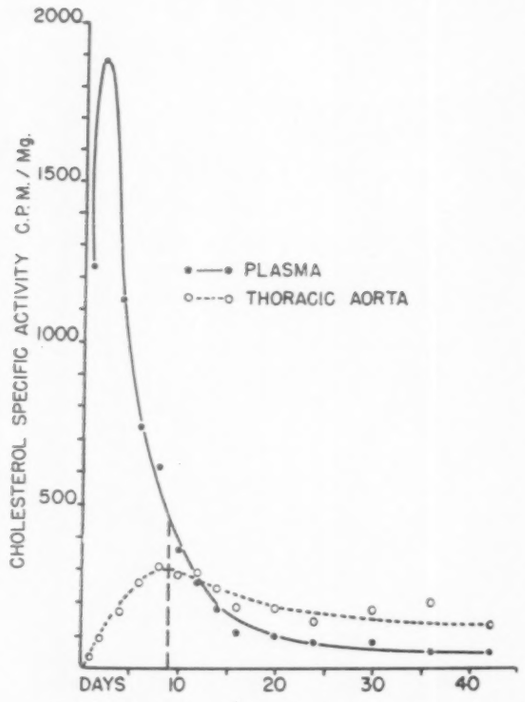


FIG. 7. Specific activities of plasma and aortic cholesterol after a single feeding of C^{14}-labeled cholesterol. (From DAYTON, S. *Circulation Res.*, 7: 471, 1959 [*23*].)

hold. For example, in the case of serum cholesterol at least two major precursors (exogeneous and endogenous) are present [*17*]. There are at least two forms of liver lecithin that turn over at different rates [*22*]. It is quite likely that as we become more familiar with the intricacies of metabolic pools we shall find many more instances of multiple precursors and non-homogeneity of metabolic pools. It may therefore be useful to determine to what extent these deviations from our assumptions interfere with the interpretation of isotope experiments. The case of multiple precursors should be discussed first and an example taken from an experiment designed to study the origin of cholesterol in normal arteries of the chick [*23*]. A single dose of C^{14}-cholesterol was fed to cockerels and the specific activities of plasma and arterial cholesterol measured at different time intervals after feeding. As may be seen from Figure 7 the specific activity-time curves of plasma and aorta do not intersect. If plasma cholesterol were the only precursor for the cholesterol in the arterial wall, and if the cholesterol in the arterial wall should comply with the assumptions made concerning the homogeneity of the metabolic pool and the randomness of cholesterol breakdown, it would be expected that the specific activity of the plasma cholesterol would equal that in the artery when the latter reached its maximum value. Therefore, it was concluded that the failure of the two curves to cross resulted from the synthesis of endogenous cholesterol by the arterial wall; this synthesis would then represent a second pathway for the appearance of cholesesterol in the artery and the arterial cholesterol would have two precursors, one labeled with C^{14} and one unlabeled. The fraction of the total cholesterol turnover accounted for by deposition from plasma is thus equal to the ratio of the peak specific activity of the arterial cholesterol to that of the plasma at the same time interval. In Figure 7 this ratio is 0.65 and the conclusion, therefore, is that 65 per cent of the arterial cholesterol was derived from plasma. From these data it cannot be ascertained whether the other 35 per cent is accounted for by continuous synthesis of arterial cholesterol from non-labeled small fragments, or whether it reflects a deposit of cholesterol which is metabolically inactive. If an investigator wished to obtain actual turnover rates of aortic cholesterol he would have to devise further experiments to distinguish between two possibilities. For example, he might administer a labeled precursor of endogenous cholesterol (acetate, mevalonic acid or squalene). From the amount of plasma C^{14}-cholesterol formed the investigator can estimate, on the basis of the previous experiment, the amount of C^{14}-cholesterol in the artery derived from deposition from the bloodstream. If after administration of the C^{14}-cholesterol precursor one finds a much larger amount of C^{14}-cholesterol in the artery than can be accounted for by deposition, the results may be justifiably interpreted as evidence for considerable cholesterol synthesis by the arterial wall.

An experiment of this type has been carried out to trace the origin of aortic phospholipids in the cholesterol-fed rabbit. First, radioactive phospholipoproteins were synthesized *in vivo* by the administration of P^{32}-phosphate to a cholesterol-fed donor rabbit, then the plasma lipoproteins were isolated twenty-four hours later. After removal of the inorganic P^{32} by dialysis the labeled lipoproteins were injected intravenously into recipient cholesterol-fed rabbits and blood samples taken for ten hours. After the ten-hour interval the aorta was removed for phospholipid analysis. From the average specific activity of

the plasma phospholipid and the amount of phospholipid P^{32} in the artery the amount of phospholipid deposited from the bloodstream per hour was estimated to be 40 μg./gm. aorta/hour [*24*].

In an accompanying experiment cholesterol-fed rabbits were injected with P^{32}-phosphate and the animals killed six hours later. From the average specific activity of plasma phospholipid and the now known rate of plasma phospholipid deposition, the amount of radioactive phospholipid in the aorta that could be expected on the basis of deposition alone was calculated. It turned out that less than 0.3 per cent of the total P^{32}-labeled phospholipid present in the artery could be accounted for by deposition and that endogenous synthesis of arterial phospholipids must therefore take place.

To confirm this finding the specific activity of aortic phospholipid six hours after injection of P^{32}-phosphate was compared with that of plasma. Since the six hour point occurs before the arterial phospholipid reaches its maximum specific activity, the specific activity of the arterial phospholipid should be less than that in plasma if the plasma phospholipid were its precursor. In the intact cholesterol-fed rabbit the specific activity of aortic phospholipid, however, is higher than that of plasma, again contradicting the hypothesis that the blood phospholipid serves as the principal precursor of P^{32}-labeled aortic phospholipids [*25*]. To strengthen the arguments derived from the specific activity gradient, several cholesterol-fed rabbits were eviscerated prior to the injection of P^{32}-phosphate. This procedure is known to suppress the incorporation of P^{32} into plasma phospholipids. In these animals with very low specific activities of plasma phospholipids the ratio of aortic phospholipid specific activity to that of plasma rose as high as 90. Moreover, although the plasma phospholipid specific activity was depressed to about one-tenth of normal, the phospholipid P^{32} in the aorta showed no depression whatsoever [*26*]. Both of these findings strengthen the conclusion that in the cholesterol-fed rabbit the majority of the phospholipid P^{32}, perhaps even all of it, is derived from synthesis *in situ*.

The evidence just presented for the synthesis of aortic phospholipid from P^{32} does not as yet allow the conclusion that the entire aortic phospholipid molecule is synthesized *in situ*. Perhaps intact phospholipid or glyceride molecules are deposited from the bloodstream, and are then subjected to rapid phosphorylation by an enzymatic mechanism. To test this possibility C^{14}-acetate was administered to intact and eviscerated cholesterol-fed rabbits [*27*]. Again the specific activity of the aortic phospholipid far exceeded that in plasma. Thus it appears that the majority of phospholipids of the aorta of the cholesterol-fed rabbit are synthesized by the aorta *de novo*.

The problems of non-homogeneous compartments and multiple precursors play a dominant role in the interpretation of these and many other such experiments. Neither the plasma phospholipid pool nor the phospholipids of aorta is composed solely of single compounds. Not only are phospholipids bound to different proteins (α, β, high and low density, etc.) but there are many different types of phospholipid in both compartments. Some studies have been made of the incorporation of P^{32} into different phospholipid fractions [*28*] and of the exchange of phospholipids between protein fractions.* None of these studies has brought forth any evidence for the existence of a very small, high specific activity fraction that could invalidate the experiments cited earlier. The possibility always exists, however, that more refined technics might uncover such a fraction.

The foregoing arguments demonstrate fairly conclusively that in atheromatous plaques of cholesterol-fed rabbits active synthesis of phospholipids proceeds. They do not, however, eliminate the possibility that the excess arterial phospholipid in atheromatous aortas was originally derived from the blood. Since the net accumulation of phospholipids in plaques is a very slow process, only a slight imbalance in the rates of deposition or synthesis and the rates of dissolution or degradation would account for the observed lipid storage. The foregoing semi-quantitative isotope experiments do not disprove the possibility that blood phospholipids gradually become incorporated into the arterial wall as part of the deposition of plasma lipoproteins and that subsequently the excess phospholipid participates in metabolic reactions (phosphorylation, acylation, etc.) of the arterial tissue at the same rate as the phospholipids "native" to the artery. It will be difficult to settle this question conclusively until more precise, quantitative isotope technics can be brought to bear on it.

* Unpublished observations.

SUMMARY

The importance of quantitative isotope technics in the study the metabolism of the whole body is discussed.

A number of simple model systems are analyzed and approximate numerical solutions are presented for the investigator who does not require the added precision of more complex mathematical analyses.

Selected examples of published data are presented to illustrate the use of the different models.

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Case Reports

Splenic Arteriovenous Fistulas as a Cause of Portal Hypertension*

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FISTULAS between the splenic artery and vein are uncommon. The first case recorded was a pathological description without clinical details by Weigert [*1*] in 1886. Goodhart [*2*] in 1889, Blakemore [*3*] in 1949, Adams [*4*] in 1951, Sigwart [*5*] in 1953, Evans [*6*] in 1954, Stener [*7*] in 1954 and Cassel et al. [*8*] in 1957 described individual cases, and the last group reviewed most of the literature.

These lesions may cause symptoms, chiefly as the result of portal hypertension, including hematemesis, melena, petechiae, ascites, and abdominal distress from the enlarged spleen. The only significant finding is the continuous murmur usually heard over the lower left posterolateral ribs, but splenomegaly, varices and hematologic abnormalities are common. Table I records the major clinical symptoms and signs, and Table II the pertinent laboratory data in the collected cases.

In the following case report, although portal hypertension was present, the dominant clinical

TABLE I
CLINICAL FEATURES OF REPORTED CASES

Author	Age (yr.) and Sex	Presenting Symptoms	Ascites	Melena and Hematemesis	Bleeding Elsewhere	Spider Angomas	Gynecomastia	Spleen	Liver	Cardiovascular	Bruit
Weigert [*1*]	49, F	Not recorded (pathological study only)									
Goodhart [*2*]	49, F	Abdominal pain and diarrhea	Yes	Yes	No	...	...	Not enlarged	Not enlarged	...	Yes
Blakemore [*3*]	23, F	Hematemesis for over 20 years	No	Yes	...	...	...	Grossly enlarged	...	...	...
Adams [*4*]		No case description "we have seen these (A-V fistulas) in the stomach, duodenum, pancreas, spleen and lung"									
Sigwart [*5*]	25, F	Hematemesis 8 years, melena for over 9 years	No	Yes	No	No	No	Moderately enlarged	Not enlarged	None	...
Evans [*6*]	67, F	Anemia and weight loss	No	No	No	No	No	Grossly enlarged	Not enlarged	None	...
Stener [*7*]	38, F	Hematemesis 8 years, melena for over 20 years	No	Yes	No	No	No	Moderately enlarged	Not enlarged	None	Yes
Cassel et al. [*8*]	34, F	Ascites	Yes	No	No	No	No	Moderately enlarged	Enlarged	None	Yes
Murray, Thal and Greenspan	18, M	Abdominal pain 8 years, bleeding	No	No	Skin and nose	Yes	Yes	Grossly enlarged	Not enlarged	Heart enlarged and systolic murmur	...

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TABLE II

LABORATORY STUDIES IN REPORTED CASES

Author	Varices	Hypersplenism	Blood Picture			Liver Function Tests						X-Ray Film	Liver Histology	Pathology
			Hemoglobin	White Blood Cells (per cu. mm.)	Platelets (per cu. mm.)	Bromsulfalein Retention	Cephalin-Cholesterol Flocculation	Thymol Turbidity	Total Protein (gm. %)	Albumin/Globulin Ratio	Alkaline Phosphatase			
Weigert [1]	No clinical information													Multiple shunts
Goodhart [2]	None	...	...	...	...	...	...	...	...	...	...	...	Clot in portal vein	Single shunt
Blakemore [3]	Yes	Yes	...	...	...	...	...	...	...	...	...	...	...	Multiple shunts
Adams [4]	No clinical information													
Sigwart [5]	Yes	No	85 %	7,200	138,000	...	...	...	...	...	...	...	...	Single shunt
Evans [6]	...	...	9.7 gm. %	4,800	...	...	...	...	...	...	...	...	...	Multiple shunts
Stener [7]	Yes	Yes	77 %	3,400	112,000	...	...	...	...	...	Normal	Aortogram positive	Normal	Single intrasplenic shunt
Cassel et al. [8]	No	No	12 gm. %	12,100	...	34% retention at 1 hr.	Negative	0	7	5/2	58 King-Armstrong units	Aortogram positive	Normal	Single shunt
Murray, Thal and Greenspan	Yes	Yes	14.1 gm. %	2,540	26,000	21% retention at 45 min.	+++	4 units	6.4	1.5/4.9	5.5 King-Armstrong units	Heart enlarged	Normal	Multiple shunts plus arterial aneurysms

picture was that of hypersplenism. The final diagnosis was made only at laparotomy, although in retrospect it should have been possible even in the absence of the characteristic murmur to have reached the correct conclusion before operation.

CASE REPORT

An eighteen year old boy was first seen at the University Hospital in 1947 at seven years of age. At his first visit to a doctor he gave a one month history of diffuse abdominal pain, and a two to three week history of fatigue associated with several daily episodes of epistaxis and a tendency to bruise easily. His doctor found that his spleen was enlarged. On examination at the University Hospital in October 1947 he had a blood pressure of 125/80 mm. Hg, a widespread harsh systolic murmur which was thought to be functional, and a firm spleen palpable 9 cm. below the left costal margin. The laboratory studies then showed a hemoglobin of 11.9 gm. per 100 ml., a red cell count of 3.5 million per cu. mm. and a white count of 4,100 per cu. mm. with 61 per cent neutrophils, 31 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The platelets ranged from 56,000 to 103,000 per cu. mm. and the reticulocyte count was 1.3 per cent. An examination of the bone marrow revealed a hyperplastic marrow with megakaryocytosis and lymphocytosis. Results of the cuff test were negative and the prothrombin time 15.5 seconds with a control of 12.8 seconds. The roentgenogram of the chest was reported as showing a questionable left-to-right shunt at the ventricular level. The esophagram revealed no abnormalities. It was thought that he was suffering from thrombocytopenic purpura and no specific treatment was undertaken or recommended.

On February 11, 1952, at twelve years of age, he was seen again at the University Hospital. In the years since his last visit he had remained well although his doctor had noted a few petechiae on the skin, a persistently low white count and hemoglobin levels below normal. He had been referred to the hospital to consider the advisability of splenectomy as a protection against traumatic rupture of the spleen. On examination he was well developed, had a blood pressure of 110/70 mm. Hg, and a few scattered petechiae on the skin. A grade 2 systolic murmur over the whole precordial area was again described. The spleen was still enlarged. The laboratory studies showed a hemoglobin of 12.5 gm. per 100 ml., a red cell count of 4.5 million per cu. mm. and a white cell count of 2,000 per cu. mm. with 51 per cent neutrophils, 36 per cent lymphocytes, 6 per cent monocytes and 7 per cent eosinophils. The platelets were 42,000 per cu. mm. and the peripheral blood smear revealed poikilocytosis, anisocytosis and ovalocytosis. Examination of the bone marrow was not different from that in 1947. The clot retraction, clotting and bleeding times were normal. There was 5 per cent retention of bromsulfalein at the end of 45 minutes. The thymol turbidity was 5 units, the cephalin-cholesterol flocculation test was 4 plus, the serum alkaline phosphatase 7.2 King-Armstrong units, the serum protein 6.7 gm. per 100 ml. with 3.1 gm. albumin and 3.6 gm. globulin. The total serum bilirubin was 0.8 mg. per 100 ml. with a one-minute fraction of less than 0.1 mg. per 100 ml. The electrocardiogram was normal, but cardiac fluoroscopy again suggested the possibility of a left-to-right shunt at the ventricular level. The esophagram was suggestive of varices. He was discharged without treatment.

On August 27, 1958, at eighteen years of age, he returned to the University Hospital complaining of several recent episodes of moderately severe pain in the mid-abdomen. Examination confirmed the previous findings. In addition he had bilateral gynecomastia, several small spider telangiectases on the chest, and 2 to 3 mm. transverse white bands on all the finger nails. The murmur was a grade 2 (6 scale) ejection systolic murmur best heard at the pulmonic area. The liver was not palpable. No Kayser-Fleischer rings could be found. The laboratory studies showed a hemoglobin of 14 gm. per 100 ml., a white cell count of 2,540 per cu. mm. with 49 per cent neutrophils, 42 per cent lymphocytes, 6 per cent eosinophils and 3 per cent basophils. The platelets were 26,000 per cu. mm. The bone marrow showed normoblastic hyperplasia with macronormoblastosis. The clot retraction, clotting and bleeding times were normal and the prothrombin time was 17.8 seconds with a control of 13.2 seconds. The bromsulfalein test showed 21 per cent retention at forty-five minutes, the thymol turbidity was 4 units and the cephalin-cholesterol flocculation test 3 plus. The serum proteins were 6.4 gm. per 100 ml. with 1.5 gm. of albumin and 4.9 gm. of globulin. The total serum bilirubin was 0.9 mg. per 100 ml. with a one-minute fraction of 0.1 mg. per 100 ml. Cardiac fluoroscopy was normal. The esophagram was again suggestive of varices.

On October 2, 1958 a cardiac catheter was passed into the vena azygos major and a retrograde venogram of this vessel and its tributaries attempted. It was hoped to demonstrate porta-systemic communications by this technic. Because of the great flow of blood in this vessel, satisfactory films could not be obtained but a blood sample was secured and noted to be more saturated with oxygen than samples from this site in normal subjects, and considerably more saturated than samples from a peripheral vein. The real significance of this finding was not suspected before operation and the saturation values were neglected until later. The diagnosis was considered to be portal cirrhosis, portal hypertension and hypersplenism secondary to hepatic disease.

A splenorenal anastomosis was planned and the patient explored on October 3, 1958. There was a



FIG. 1. Photograph of the hilum of the spleen showing the aneurysm and the dilated splenic artery.

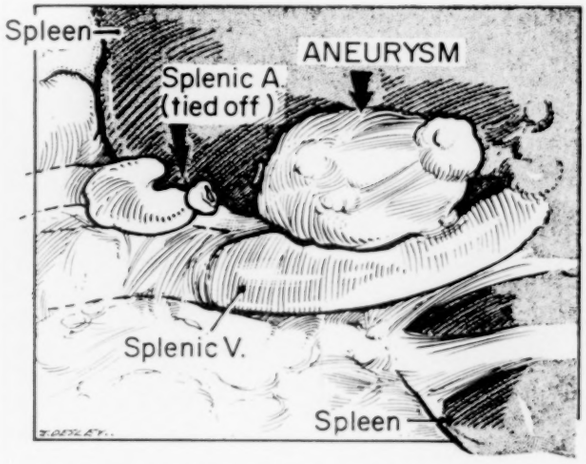


FIG. 2. Labelled drawing of Figure 1.

large spleen surrounded by big, thin-walled veins running from the hilum of the spleen to the adjacent diaphragmatic and retroperitoneal veins, some of which were more than 1 cm. in diameter. The striking findings, however, were two arteriovenous fistulas between the splenic artery and vein. (Figs. 1 and 2.) No portal vein could be seen or felt, and injection of radiopaque material into the splenic vein failed to fill the portal vein, but the dye appeared to course upward into the azygos system. (Fig. 3.) Near the hilum of the spleen there was a large aneurysm of the splenic artery which communicated with the splenic vein, and over which a thrill could be felt. (Figs. 4 and 5.) There was a smaller fistula between a branch of the splenic artery and a tributary of the splenic vein at the superior pole of the spleen. A direct pressure measurement in the splenic vein was recorded as 38 cm. (citrate solution). The splenic artery was tied proximal to the aneurysm and the pressure in the splenic vein fell to 28 cm. The spleen was then removed and many of the collateral veins were ligated, leading to a rise in pressure in the splenic vein to 38 cm. A splenorenal anastomosis was carried out, the splenic vein pressure finally falling to 28 cm. A biopsy of the liver was obtained at the time of operation. Although the spleen was enlarged, histologic examination was essentially within normal limits. The liver itself appeared small in size but normal in consistency, and microscopic sections showed no evidence of disease. Immediately after operation the arterial system of the spleen was injected with radiopaque material, and roentgenograms revealed numerous berry aneurysms at the bifurcations of the intrasplenic arteries. (Fig. 6.)



FIG. 3. X-ray film taken after the injection of radiopaque material into a tributary of the splenic vein, showing a large collateral vein coursing from the hilum of the spleen along the subcostal margin to join the azygos system and to fill some of the esophageal varices.

The patient did well postoperatively. The saturation values for the venous samples (which were not reported before the operation) were approximately 86 per cent for the vena azygos major. Two months after the operation the white count and platelets were normal. On June 1, 1959, eight months after surgery, the laboratory data revealed a hemoglobin of 14.7 gm. per 100 ml., a white cell count of 5,450 per cu. mm. with a differential count of 34 per cent neutrophils,



FIG. 4. The arterial end of the aneurysm has been opened and a probe passed through the fistula into the splenic vein.

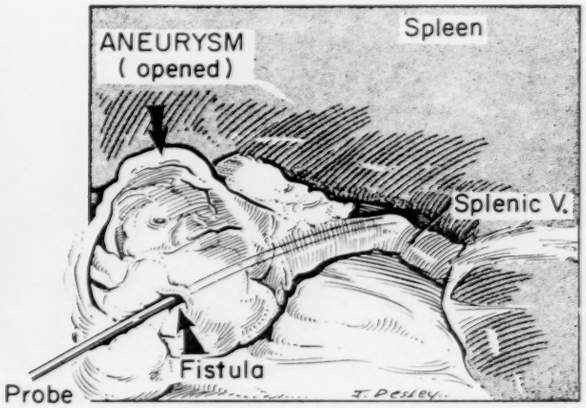


FIG. 5. Labelled drawing of Figure 4.

56 per cent lymphocytes, 3 per cent monocytes, 6 per cent eosinophils, 1 per cent basophils, and a platelet count of 459,000 per cu. mm. The prothrombin time was 14.8 seconds with a control of 12.8 seconds. There was 21 per cent retention of bromsulfalein at the end of forty-five minutes, the thymol turbidity was 3 units and the cephalin-cholesterol flocculation test was 3 plus. The serum proteins were 7.3 gm. per 100 ml. with 3.3 gm. of albumin and 4 gm. of globulin. The total serum bilirubin was 0.8 mg. per 100 ml. with a one-minute fraction of less than 0.1 mg. per 100 ml. The roentgenogram of the chest and the esophagram were normal.

He felt well and his appearance was good. Gynecomastia was still present. No spider angiomas were visible. The transverse bands on the nails were gone. The liver was not palpable.

COMMENTS

Although this is a rare anomaly, it should be suspected in all cases of portal hypertension, especially in young people who have long histories dating to early childhood. The combination of portal hypertension, hypersplenism, and a small liver with relatively normal liver function tests should encourage a search for the characteristic continuous murmur over the posterior aspect of the spleen. If such a murmur is heard or if the circumstances described are present, aortography should be undertaken to outline the fistula.

The fistulas may be congenital or acquired. The acquired group may result from trauma, as in the case of Cassel et al. [8] in which the injury was due to a rifle bullet, or may result from spontaneous rupture of an existing aneurysm of the splenic artery into the splenic vein. There are many reports of aneurysms of the splenic artery rupturing and producing retroperitoneal hemorrhage, especially during labor or in the later months of pregnancy. It is quite possible that the rupture might occasionally occur into the splenic vein, producing a fistula. Eight of the nine cases described have occurred in women, a fact suggesting that pregnancy may be related to the onset of symptoms, and thus to the rupture of an existing aneurysm into the vein. No men-



FIG. 6. X-ray film of a postoperative injection of the splenic artery with radio-opaque material showing multiple aneurysms of the splenic arterial tree. Most of these appear to be at the bifurcation of the vessels.

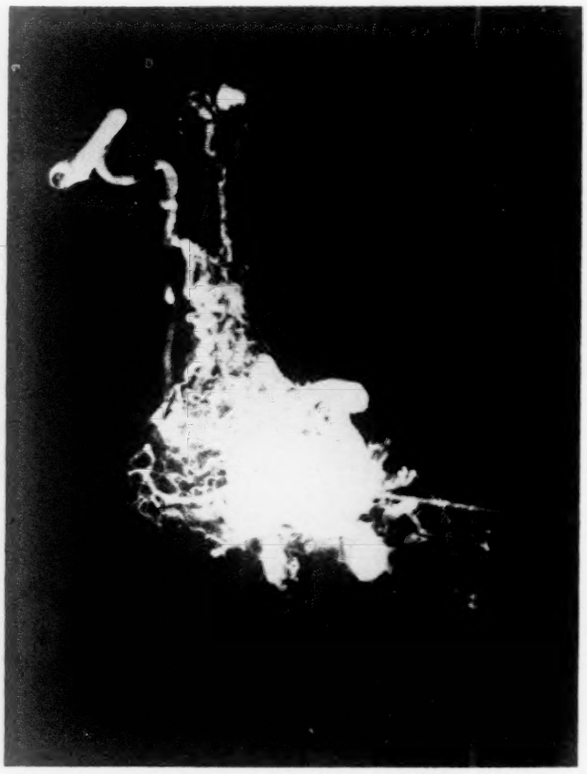


FIG. 7. X-ray of esophageal varices (injected with radiopaque material) produced experimentally in the dog by means of a splenic arteriovenous fistula and progressive occlusion of the splenic vein.

tion of the relation of pregnancy to the onset of symptoms was made in the reviewed case reports except in Cassel et al. [8]. In their patient, symptoms appeared two months after delivery.

Symptoms beginning in early life and the finding of multiple fistulas would certainly bespeak the likelihood of a congenital origin for some of the patients. In our patient the two fistulas, the multiple small aneurysms of the intrasplenic arterial tree, and the symptoms of portal hypertension and hypersplenism at seven years of age strongly suggest the congenital nature of this lesion.

It is certain that splenic arteriovenous fistulas produce portal hypertension in man. Both Sigwart [5] and Blakemore [3] have recorded abnormally high pressures in the splenic vein or its tributaries in such cases. The experimental production in animals of chronic extrahepatic portal hypertension with varices, however, is difficult [9]. Simple splenic arteriovenous or splenoportal arteriovenous shunts [10] do not produce sustained portal hypertension in animals, but merely actively congest the liver. In animals, chronic progressive obstruction of the portal vein leads only to a temporary rise in portal vein pressure which returns to normal in a week or more, probably because of the development of adequate collaterals [11].

Tamiya and Thal [12], of the Department of Surgery of the University of Minnesota, working with dogs, have been able to reproduce a situation similar to that described in our patient. A splenic arteriovenous fistula is established and followed by slowly progressive occlusion of the portal vein or of the splenic vein proximal to the fistula. The extensive collaterals to the azygos system and the esophageal varices which develop can clearly be seen on x-ray films after injection of the coronary vein with radiopaque material or on injection of animals at postmortem examination. (Fig. 7.) Pressures recorded in the splenic vein or in the collaterals of the splenic venous system remain persistently above normal levels.

In the cases of Goodhart [2] and Cassel et al. [8], in which ascites was prominent and portal hypertension minimal, extensive collaterals were not demonstrated, and this finding is in keeping with the report of Baggenstoss and Wollaeger [13] who studied cases of extrahepatic portal vein occlusion, and suggested that ascites was more likely to develop when the collateral circulation was poorly developed. Sigwart [5] recorded the only positive identification of the portal vein at operation on a splenic arteriovenous fistula, when he mentioned that it was enlarged. In the case report of Cassel et al. [8] the grossly enlarged liver would point to patency of the portal vein. In our patient the portal vein could neither be located nor demonstrated by venography. It can only be assumed that it was hypoplastic or absent, accounting for the small size of the liver despite the magnitude of the shunt, and for the presence of the cardiac findings which had not been noted in any of the previously reported cases. This finding would also support the congenital origin of the syndrome.

The oxygen saturation of the blood in the vena azygos major rises steeply following the procedure of Tamiya and Thal [12], suggesting the possibility that the determination of oxygen saturation at this site might provide evidence of shunting if hepatic disease is not believed to be the major problem. The blood oxygen saturation of the portal vein is higher than the peripheral venous blood saturation in the systemic circuit

in normal subjects, either because less extraction of oxygen occurs in the splanchnic bed or because arteriovenous shunting occurs normally in the gut [*14,15*]. In cases of cirrhosis the portal venous blood saturation is even higher than in normal subjects [*16*] and Evans blue dye, injected into the hepatic artery, makes an early appearance in the portal vein [*17*]; both of these facts support the probability of shunting of hepatic arterial blood into the portal venous system. When we found that the blood from the vena azygos major looked highly saturated with oxygen we accepted this as evidence of just such a mechanism, concluding that the hepatic artery blood was reaching the azygos vein by collaterals from the portal vein [*18*]. Had we known, however, that the saturation was as high as 86 per cent we might have been reluctant to accept this as the sole explanation.

Cardiac signs have been singularly absent in all cases except our own. In our patient the circulation was often noted to be hyperdynamic, the pulse being full and at times distinctly of water-hammer quality. A systolic ejection murmur was heard and roentgenograms of the chest and fluoroscopy were reported as showing slight generalized cardiac enlargement, with increased vascularity of the lungs, suggestive of an interventricular septal defect. These findings were too easily attributed to the hyperdynamic circulatory state, well recognized in cirrhosis and thought to result from peripheral vasodilatation or the opening up of pre-existing arteriovenous shunts in the liver and elsewhere in the body in response to the release of some unknown humoral factor [*19*]. The only morphologic difference between our patient and the others was the presence in ours of portal vein hypoplasia, which would mean that most of the arterial blood would be shunted directly into the azygos system without the interposition of the protective barrier of the liver. Sigwart [*5*] measured the total red cell mass and total blood volume by the P^{32} method in his patient and found that, unlike a true systemic arteriovenous fistula, the total blood volume was not increased. This would suggest that the liver did indeed offer a resistance to the increased flow in the portal vein and thus protect the systemic circuit from overloading.

In retrospect, it is obvious that on the first two admissions of our patient to the hospital the hepatic function was not sufficiently disturbed to invoke primary disease of the liver as the cause of the circulatory changes. Childs [*17*] has shown that temporary occlusion of the portal vein causes prompt reduction in the intrahepatic portal venous pressure, so that the abnormal results of liver function tests on the third admission might possibly be the result of inadequate perfusion of the liver, both with portal venous blood and with hepatic arterial blood. The last might result from the lower resistance to flow in the splenic artery than in the hepatic artery, permitting greater flow in the former vessel and reduced flow in the latter. The improvement in liver function tests after operation suggests the possibility of improved hepatic artery flow. The gynecomastia and spider angiomas might have resulted from estrogenic substances by-passing the liver and thus avoiding metabolic alteration.

SUMMARY

A patient with splenic arteriovenous fistula associated with portal vein hypoplasia, presenting as hypersplenism, is reported on herein and reports of eight other cases of splenic arteriovenous fistulas are reviewed. The diagnosis in our patient was not made until operation, when the fistula was excised, the spleen removed, and a splenorenal shunt performed. The intrasplenic arterial tree showed numerous aneurysms at the bifurcation of the vessels supporting the congenital nature of the lesions.

Catheterization of the vena azygos major was successfully performed before operation and the oxygen saturation of the sample obtained found to be unusually high. These results were not interpreted correctly but believed to support the possibility of shunting of portal venous blood into the azygos system.

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Cryoglobulinemia*

Rationale of Treatment of a Case Based on Unusual Properties of the Cryoprotein

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ABNORMAL plasma globulins which precipitate on cooling were first termed cryoglobulins by Lerner and Watson [*1*]. The disease entities in which such proteins are found and studies on the correlation between the chemical properties of the proteins and the clinical syndrome produced have been reviewed by Volpé et al. [*2*] and Mackay et al. [*3*].

This report describes herein a patient who has a cryoglobulin with unique properties; it is stabilized *in vivo* and *in vitro* by basic organic amines; it has a long turnover time, with a half-time of nineteen days; and it has been reduced in amount, with subsidence of the usual clinical findings, by repeated plasmapheresis. A more detailed report of the properties of the cryoglobulin will be presented elsewhere [*4*].

CASE REPORT

A. E., a forty-eight year old Swedish businessman, was first seen on June 17, 1957, after a marrow aspirate had been said to show plasmacytic myeloma. The referring physician was reluctant to accept this diagnosis because of the atypical clinical features. The patient dated the onset of his illness to 1953, when he began having epistaxes. Bleeding was self-limited at first, but recurred at decreasing intervals and had required nasal packs or cautery for control on numerous occasions during the preceding two years. In 1955 he began to have episodic bleeding from his gums. A barium meal in 1956 revealed deformity of the duodenal cap; this study was occasioned by the occurrence of melena although the patient denied ever having had intolerance to food, heart burn, nausea or vomiting. He had followed a modified Sippy program since then. Since 1956 he had also had a twenty-four-hour episode of gross hematuria and had noted that he bruised easily and that prolonged bleeding occurred from minor cuts. In addition, he complained of fatigability, mild exertional dyspnea and visual impairment, all of two years' duration. Exposure to cold increased all of these symptoms; and he described a painless, bluish discoloration of hands, nose and ears which followed such exposure. On specific questioning, he denied skeletal pain; and recent roentgenograms of the skeleton were reported to reveal no abnormalities.

Physical examination revealed a 185 pound, well nourished white man who did not appear ill. Faint cyanosis was seen in fingers and feet, and there were spider angiomas and prominent capillary circulation over the face and collar area. Optic fundi showed greatly distended, tortuous veins with "sausage-like" indentations where arterioles intersected their course. Flame-shaped and well demarcated hemorrhages were seen in both fundi. The blood pressure was 146/98 mm. Hg. The liver was palpable 3 cm. below right costal margin, and the spleen extended 1 cm. below left costal margin. No other abnormalities were found.

Initial laboratory studies were as follows: hemoglobin, 10.6 gm. per 100 ml.; erythrocytes, 4.1 million per cu. mm.; hematocrit, 29.5 per cent; leukocytes, 6,100 per cu. mm., with 35 per cent segmented neutrophils, 4 per cent eosinophils, 38 per cent lymphocytes, 8 per cent monocytes and 15 per cent disintegrated cells; reticulocytes, 1.3 per cent; and thrombocytes, 133,000 per cu. mm. The marrow was normal in cellularity and cellular composition except for the presence of 7 per cent mature plasmacytes. The results of urinalysis were normal. The blood urea nitrogen was 18 mg. per cent; thymol turbidity, 3.4 units; bromsulphalein, no dye retained at forty-five minutes. The serum total protein was 12.2 gm. per cent, of which 9.3 gm. was globulin. The serum bilirubin was 0.6 mg. per cent. The results of Kahn and Kline tests for syphilis were negative.

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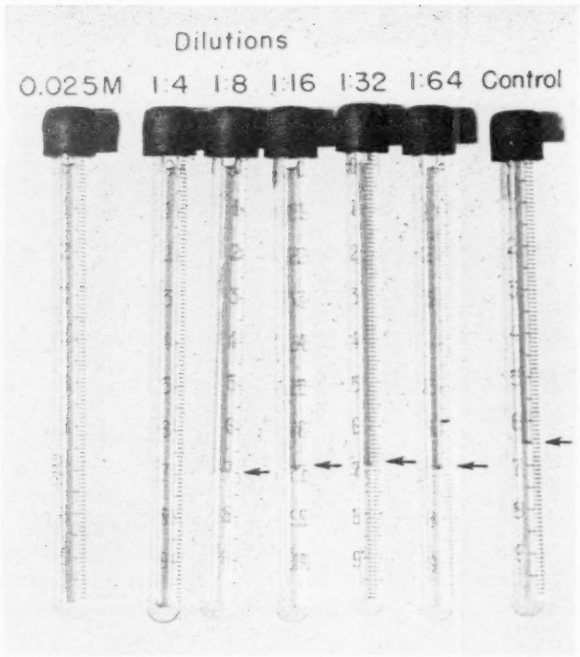


FIG. 1. The effect of *in vitro* addition of lysine to heparinized plasma at a temperature of 4°C. in preventing cold precipitation of cryoglobulin. Lysine was added to a final concentration in plasma of 0.025 M and serial dilutions of this concentration of lysine were added to replicate volumes of plasma.

Special Studies. A number of special studies were made. The methods used are those cited in the references or described in the section below.

After standing at 4°C., the patient's plasma contained a clear, gelatinous precipitate which made up 40 to 55 per cent of the plasma volume. The gel completely redissolved when the plasma was warmed to room temperature, and this process could be repeated with the same sample and with all subsequent samples of plasma. When the temperature was carefully regulated over a range from 37° to 4°C., gelation started at 26°C.

Dialysis of the patient's plasma against 0.9 per cent sodium chloride preparatory to Tiselius electrophoresis shifted the critical temperature of gelation to 37°C. It was assumed that a dialyzable solute or solutes which acted to stabilize the abnormal protein in solution had been removed. *In vitro* studies were made to test this hypothesis by adding a number of solutes to the patient's native plasma. Of over 110 solutes tested, many were found to have such an effect [*4*]. Glucose and urea, added to a concentration of 1 M, prevented gelation at 4°C. Amino acids were also effective but differed in degree; glycine at a concentration of 0.5 M prevented gelation; basic amino acids such as lysine and ornithine were the most effective, preventing gelation at 6×10^{-3} M. Figure 1 illustrates one such *in vitro* study. No gel formed in the tubes containing lysine in a concentration higher than

TABLE 1
EFFECT OF LYSINE ON CLOTTING TESTS

Clotting Tests (April 10, 1958)	Native Plasma	Plasma Plus 0.0063 M Lysine
Prothrombin and proconvertin	9%	80%
Proaccelerin	5%	80%
Quick prothrombin time	no clot	13.8 sec.
Partial thromboplastin	no clot	66.5 sec.

0.00625 M. All tubes containing smaller amounts of lysine showed some gel formation after standing twelve hours at 4°C., but somewhat less than was found in the control tube containing untreated plasma.

Repeated cold precipitation of the supernatant plasma removed most but not all of the abnormal protein. Similarly, addition of bovine thrombin to the patient's plasma (133 units per 20 ml. of plasma) resulted in a gelatinous clot which did not retract. The clotted material was removed by centrifugation at 1,500 r. p. m. for thirty minutes and the supernate reclotted twice with thrombin, with the removal of coagulated protein by centrifugation. The final supernate was exhausted of clottable protein on further addition of thrombin but still contained cryoprotein, as determined by cold precipitation and paper electrophoresis.* The three coagulated sediments were pooled and dehydrated by successive washing with saline solution, ethanol and ether; the weight indicated a clottable protein content equal to 3.4 gm. per 100 ml. After addition of lysine (6×10^{-3} M) to the patient's plasma, the amount of protein coagulated by thrombin fell to 350 mg. per 100 ml., presumably representing the true fibrinogen content.

In a number of clotting systems, the end point was markedly prolonged or absent. This was true as long as the amount of cryoprotein was high, i.e., 7 to 9.5 gm. per cent. Table 1 gives the results of several clotting tests made in replicate on the patient's native plasma and on plasma to which lysine had been added to a concentration of 6×10^{-3} M. The results of tests designed to measure prothrombin and proconvertin [*5*], proaccelerin [*6*], the Quick one-stage system [*7*] and the partial thromboplastin time [*8*] were restored from markedly abnormal to normal by the addition of lysine. In the thromboplastin generation test, modified by substituting asolectin for platelets [*9*], the results of the patient's serum and plasma were normal. No clot retraction occurred in the patient's whole blood; but retraction was normal in blood

* Using Spinco model R unit with 0.075 M barbital buffer at pH 8.6 and for sixteen hours at a current of 5 milliamperes.

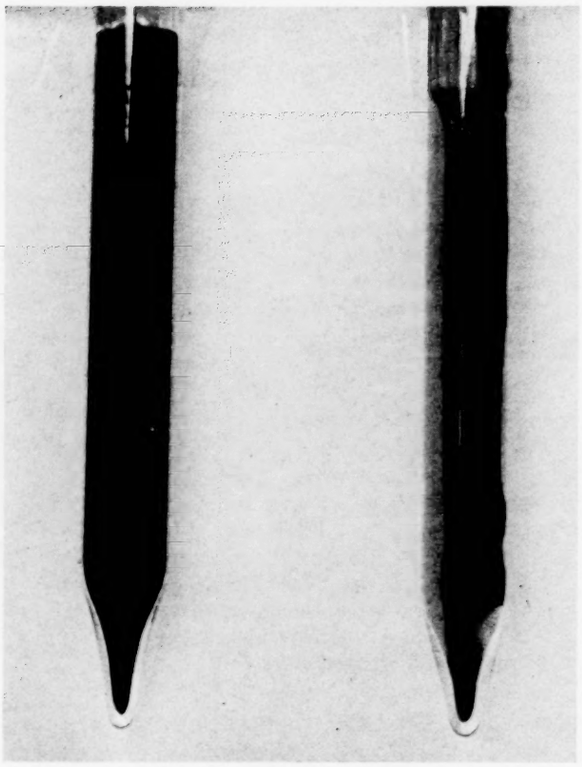


FIG. 2. The effect of lysine on clot retraction at three hours. *Left*, no lysine. *Right*, 0.0063 M L-lysine.

enriched with lysine to 6×10^{-3} M, as illustrated in Figure 2.

The electrophoretic pattern of patient's serum containing 0.0625 M lysine is shown in Figure 3. Ultracentrifugal studies [*4*] indicate that the abnormal protein is not a macroglobulin.

The patient's blood viscosity was markedly increased, correlating with the amount of cryoprotein. The method used [*10*] permits measurement of the viscosity of heparinized plasma or of whole blood without anticoagulants. The initial whole blood viscosity was 25, or at least five times that of normal blood [*10*], and the plasma viscosity was 18, or at least ten times that of normal plasma. The effect of this increased viscosity could be visualized by biomicroscopy of conjunctival vessels. There was marked engorgement of the capillaries, only a few of which had visible motion of red cells, and these showed marked sludging and slow rate of flow.* The circulation time, using Decholin,® was normal, however, suggesting that only the peripheral blood flow was impaired.

The *in vivo* effect of two amino acids found to prevent gelation *in vitro* was tested. Figure 4 illustrates the effect of intravenous infusions of 40 gm. of arginine in two separate studies and of 40 gm. of lysine,† after a

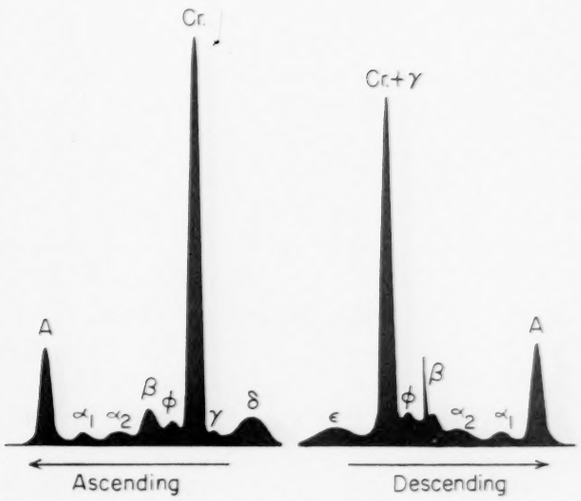


FIG. 3. Electrophoretic pattern of patient's serum containing 0.0625 M lysine.

base-line infusion of saline solution, in a third such study. In addition to the change in plasma viscosity and in the amount of cold precipitate, as illustrated, capillary blood flow observed by biomicroscopy of the conjunctival vessels was followed. A definite though transient improvement in all three parameters was observed during the infusion of arginine; a more impressive change was seen during the infusion of lysine. The patient had no untoward effects during these infusions. Following all three studies there seemed to be a rebound phenomenon with increase in viscosity and cryocrit* above base-line values and for this reason we have not pursued this approach in therapy.

A nitrogen balance study was undertaken from June 11 to July 20, 1958 in an attempt to determine the effect of negative nitrogen balance on the amount of abnormal protein. This study is presented in Figure 4. After a preliminary three-day period of hospitalization the patient was given a 2,040 calorie diet, with 250 gm. of carbohydrate, 90 gm. of protein, and 80 gm. of fat during periods 2 and 4. During period 3 he received a diet of 1,720 calories with the same amounts of carbohydrate and fat but only 10 gm. of protein. Standard balance technics [*11*] were used. He had received a therapeutic trial of prednisone therapy during a ten-month period prior to this study without apparent effect on the course of his disease or the amount of abnormal protein. This medication was continued in a dose of 35 mg. daily during the study. As noted in Figure 5, he lost 4.4 kg. of weight and was in slightly negative nitrogen balance during period 2; at the same time there was a progressive increase in concentration of the cryoprotein which reached a maximum of 9.3 gm. per cent at the end of this period. During period 3, while eating only

* Drs. John Harris and Walter Enders did the biomicroscopic observations.

† Supplied by Pfizer Laboratories.

* Cryocrit is the relative volume of gel present in heparinized plasma after twelve hours at 4°C.

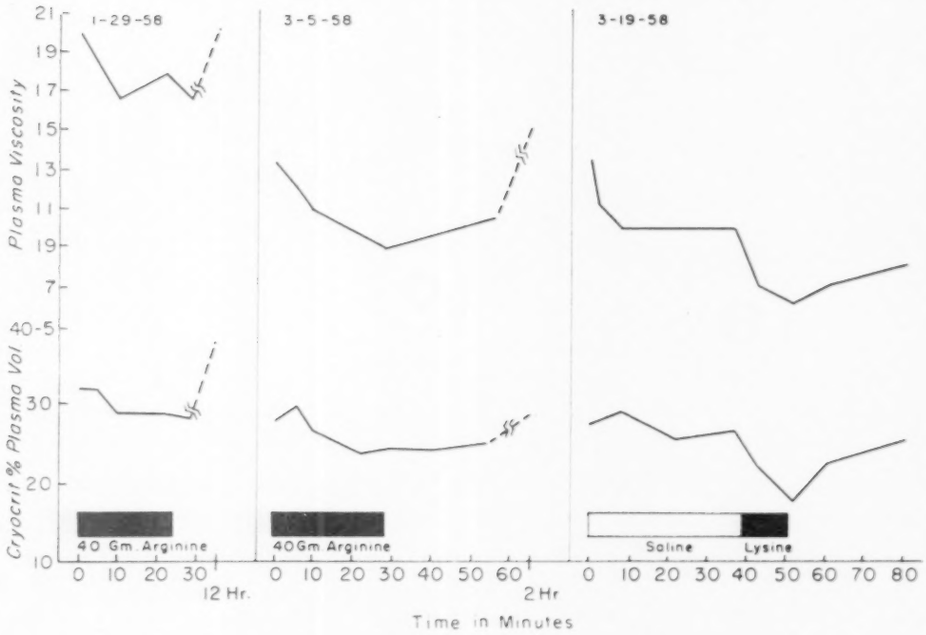


FIG. 4. The effect of infusions of arginine and lysine on viscosity and cryocrit.

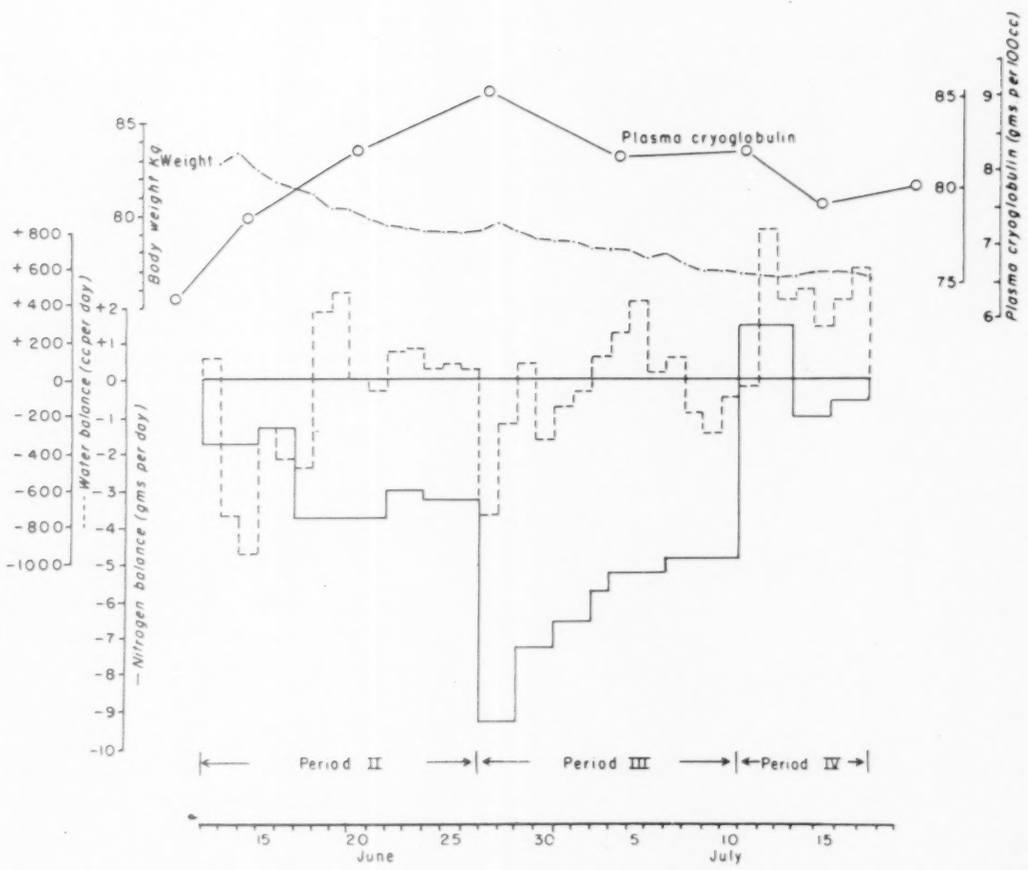


FIG. 5. Change in concentration of cryoglobulin during negative nitrogen balance.

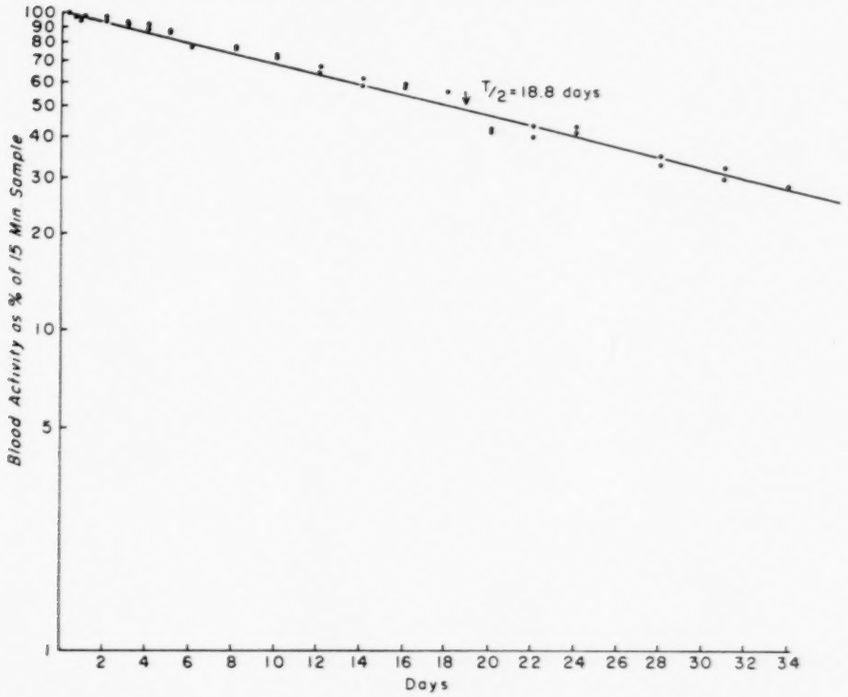


FIG. 6. Turnover time of cryoglobulin labelled with I^{131}.

10 gm. of protein per day, he lost an additional 2.6 kg.; he was in more negative nitrogen balance, and there was a fall in the concentration of the abnormal protein. Finally, during period 4, his weight stabilized; and there was a further fall in the concentration of cryoprotein. Water balance, as charted, represents measured intake minus output and an estimated 800 cc. per day for insensible loss.

Repeated precipitation of the cryoglobulin by dialysis at 4°C. resulted in preparations which were pure, as judged by electrophoretic and ultracentrifugal homogeneity [*4*].

Immunologic studies were made of the purified cryoprotein. The gel was dissolved in 1 M sodium chloride and serial dilutions made. Using rabbit antihuman fibrinogen serum, precipitin tests were performed and the results were negative. Similar studies using rabbit anti-human gamma globulin serum gave positive reactions with cryoprotein concentrations as low as 0.6 mg. per cent. Several rabbits were immunized with the purified cryoprotein, using Freund adjuvant and 50 mg. cryoprotein per rabbit. The antiserum produced gave positive precipitin reactions with the cryoprotein at concentrations of 0.6 mg. per cent. In addition, positive precipitin tests were obtained with human serums and plasma diluted 1:3,200 and with human gamma globulin at concentrations of 1.2 mg. per cent. Neutralization studies were carried out by mixing the rabbit cryoglobulin antiserum at a 9:1 ratio with human serums and human gamma globulin (1 per cent solution). The rabbit cryoglobulin antiserum treated with human serums no longer reacted with the human serums, plasma, or gamma globulin in a precipitin test, but would react with the cryoprotein at concentrations as low as 1.2 mg. per cent. The rabbit cryoglobulin antiserum mixed with human gamma globulin no longer reacted with human gamma globulin. However, positive precipitin tests were obtained with human serums or plasma at dilutions of 1:400 and with cryoprotein concentrations as low as 2.5 mg. per cent.

A sample of purified cryoglobulin labelled* *in vitro* with I^{131} was given intravenously to the patient at the start of period 2 during the nitrogen balance study. The rate of disappearance of radioactivity from the patient's circulation (Fig. 6) followed an exponential slope, with a half-time of 18.8 days. The volume of distribution of the iodinated protein was 9,470 cc.

The long turnover time of the cryoglobulin led us to treat the patient over a one-year period by removal of 250 to 750 cc. volumes of plasma at two- to six-week intervals. Figure 7 presents serial observations of the plasma viscosity, concentration of cryoglobulin, and cryocrit during this period of plasmapheresis. There has been a progressive fall in all three parameters. Clinically, the patient has noted increased strength and has had no further bleeding. The results of all tests of his clotting system have been normal since the concentration of cryoglobulin has been lower than 7 gm. per cent. There has been no significant change in other serum proteins, except that oral supplementation with 33 gm. of a protein hydrolysate daily was

* Labeling by Abbott Laboratories, Chicago, Illinois.

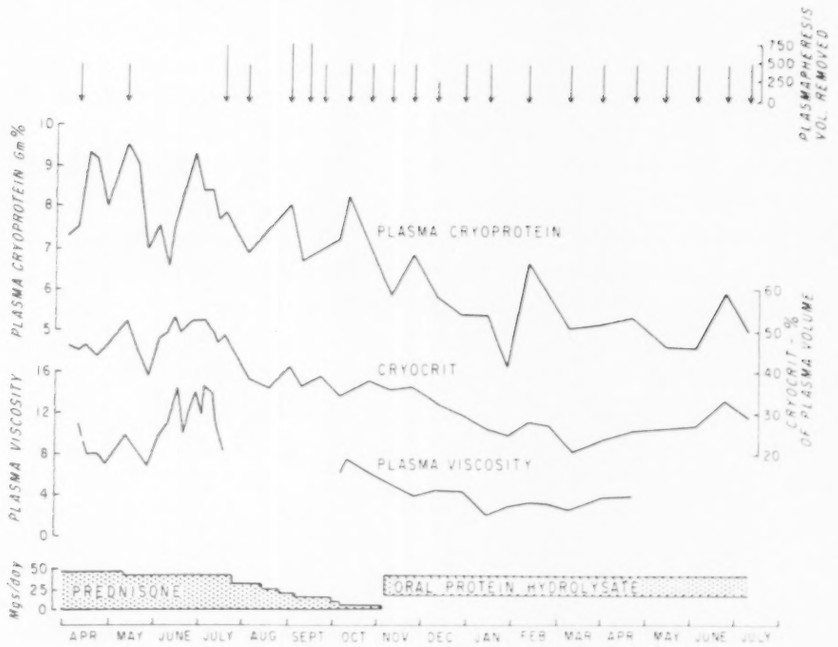


FIG. 7. The effect of plasmapheresis on the concentration of cryoglobulin, plasma viscosity and cryocrit.

begun in November 1958, because of a fall in serum albumin from 2 to 0.7 gm. per cent. Albumin values since then have stabilized at 1.5 to 2 gm. per cent, which was the same range of concentration found before plasmapheresis. His hemoglobin has increased to and remained at normal values; his weight is constant; and his peripheral circulation, as seen by biomicroscopy, has improved as have his peripheral cyanosis and the prominent capillary bed and spider angiomas over his face and neck. Blood volume, as measured with Cr^{51}-labeled erythrocytes [*12*], was 7,600 cc. (85 cc./kg.) before plasmapheresis and decreased to 6,760 cc. (82.5 cc./kg.) six months after plasmapheresis was begun. The change reflects decrease in plasma volume which dropped from 5,660 cc. (63.2 cc./kg.) to 4,260 cc. (52 cc./kg.). Repeat marrow studies have shown no change, skeletal x-rays still show no abnormalities, and the spleen is no longer palpable.

COMMENTS

Cold precipitation of the abnormal protein in this patient can be prevented *in vitro* by basic amines, which are believed to interfere directly or indirectly with hydrogen bond formation [*4*]. The gel that forms in the absence of such stabilizing agents is held together by weak hydrogen bonds. Polymerization of activated fibrinogen to fibrin has also been shown to depend in part on hydrogen bonds [*13,14*]. Our data indicate that the cryoglobulin described here copolymerizes with fibrinogen, causing a loose gel rather than the normal fibrin clot, accounting for the clinical and laboratory abnormalities in clotting. Henstell and Kligerman [*15*], on the basis of more elaborate studies, have postulated interference with the clotting mechanism by unusual plasma globulins which complex with and/or coprecipitate factor V (proaccelerin), factor VII (proconvertin) and prothrombin. Since the end stage for all these clotting systems depends on the formation of a fibrin clot, it is possible that these workers were observing, but otherwise interpreting, the same protein-fibrinogen interaction demonstrated in our patient. Firkin [*16*] has also presented data indicating coprecipitation of fibrinogen and an abnormal cryoglobulin.

The increased viscosity and slowed peripheral circulation probably reflect some degree of polymerization of the abnormal protein even at body temperature, since these effects are also decreased by *in vivo* infusion of arginine and lysine. The effect of blood viscosity on hemodynamics has been studied by Seligman, Frank and Fine [*17*]. They point out that in tourniquet shock, which is associated with an elevated blood viscosity, restoration of blood volume is more important than the correction of viscosity. At least one compensatory mechanism which probably operated in our patient was an increase in plasma volume. Following plasmapheresis, with

decrease in the concentration of cryoglobulin from 9.5 to 4.4 gm. per cent, there was a decrease in plasma volume from 63.2 to 52 cc. per kg. body weight, which accompanied the amelioration of symptoms, signs and abnormal laboratory findings.

The site of production of the cryoglobulin is unknown, but is presumed to be the plasmacytes [*3*]. Immunologic studies indicated a cross reaction with antiserums against normal gamma globulin, but also a specific antigenic reaction peculiar to this patient's abnormal protein. Similar immunologic specificity of the abnormal proteins in myeloma and macroglobulinemia has been supported by some [*17–21*] and not by other [*23–25*] workers. The former group favor the concept that these proteins result from aberrant protein synthesis of paraproteins similar but not identical to their normal counterpart. If the basic change is a neoplastic alteration of the plasma cell, as is thought to be true in myeloma, the rate of production of the abnormal protein might be expected to be autonomous and to occur at the expense of the synthesis of normal proteins. An alternative hypothesis is that the abnormal protein accumulates because it lacks normal structure and function. This latter concept would not imply a priority for synthesis and would suggest that removal of the abnormal protein might correct the clotting defects and viscosity. Barr et al. [*26*] and Skoog and Adams [*27*] also have used plasmapheresis in treating patients with abnormal proteins.

The nitrogen and water balance studies reported here suggest that the synthesis of cryoglobulin may have decreased during a period of negative nitrogen balance, as judged by a fall in concentration. Unfortunately, blood volume was not measured during this study, and it is impossible to relate the change in concentration solely to decreased synthesis, since changes in fluid balance also were occurring. The negative water balance early in period 2 may account for the rise in cryoglobulin concentration and the positive water balance during period 4 for the further decrease in concentration after an initial drop most probably due to the negative nitrogen balance in period 3.

The turnover time of the cryoglobulin in our patient with a half-time of 18.8 days is considerably longer than the half-time of 13.1 days reported by Dixon et al. [*28*] for iodinated human gamma globulin and is about the same as the eighteen day half-time reported by London [*29*], who used *in vivo* labeling of human gamma globulin with N^{15}-glycine. Our half-time of 18.8 days probably underestimates the actual turnover time of the cryoglobulin. Knowing the patient's blood volume and assuming a half-time of 18.8 days and a constant rate of production, it can be calculated that at least biweekly removal of 500 cc. of plasma would be necessary to lower the concentration from 9.5 to 4.4 gm. per cent. It may be inferred, therefore, that this protein is even more slowly catabolized than our turnover estimate would indicate or that plasmapheresis has somehow interfered with the rate of synthesis.

SUMMARY

The studies of a forty-eight year old man who has a cryoglobulin with unique properties are presented herein. The cryoglobulin polymerizes to form a gel which interferes with the blood clotting test systems, causes increased blood viscosity, and slows peripheral circulation. The mechanism of these effects is related to hydrogen bond formation, which can be prevented *in vivo* and *in vitro* by basic organic amines. The protein has a long turnover time with a half-time of 18.8 days. It is related immunologically to gamma globulin but also has a specific immunologic reaction. Nitrogen balance studies showed a decrease in the concentration of cryoglobulin when the patient was in negative nitrogen balance. Removal of the abnormal protein by plasmapheresis resulted in lowering of the concentration from 9.5 to 4 to 5 gm. per cent and correction or improvement of all abnormal clinical and laboratory findings.

ADDENDUM

In August 1959, the patient had a temperature of 102°F., malaise, and aching pain in his arms and legs. He had no localizing signs of infection, and he improved after several days of tetracycline therapy. Fever and night sweats recurred transiently in September and subsided without therapy. On October 22, 1959, he was hospitalized because of a second recurrence of fever and malaise. Physical findings were unchanged. Blood cultures were positive for gamma streptococcus; after an initial response to penicillin and streptomycin therapy, hypesthesia of the left side developed on November 12, 1959. Within a few hours he became comatose with generalized rigidity, hyperreflexia, and bilateral Babinski reflexes. Generalized convulsions ensued and he died.

Autopsy demonstrated a massive intracerebral and intraventricular hemorrhage, subacute bacterial endocarditis involving the pulmonary and mitral valves, and mild thickening of the mitral and aortic valves consistent with old rheumatic disease. Organ weights were as follows: liver 2,500 gm.; heart 470 gm.; kidneys, right 220 gm., left 210 gm.; and the spleen 620 gm. Lymph nodes and thymus were described as slightly enlarged. There were no skeletal lesions. Marrow, spleen, and lymph nodes contained some increase in mature plasmocytes but showed no other abnormality.

Cerebral blood vessels were carefully dissected and showed no evidence of aneurysm or septic embolus. Hemorrhage occurred in the region of the right middle cerebral artery.

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Embolic Osteomyelitis of the Spine as a Complication of Infection of the Urinary Tract*

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THE alteration of patterns of bacterial infection [*1*] and susceptibility of the host [*2*] attendant upon the use of antibiotics and steroids has focused attention on many formerly infrequent complications, notably those due to resistant strains of staphylococci and enteric bacilli [*3,4*]. There has also been an increase in the importance of the genitourinary tract as a portal of entry, partly because of the nature of the organisms involved and the frequency with which instrumentation and manipulation [*5*] in this area renders it vulnerable to them. The present report deals with two cases representing an unusual complication of generalized infection initially localized to the genitourinary tract, namely, embolic osteomyelitis of the spine. In one instance the organism responsible was hemolytic Staphylococcus aureus; in the other it apparently was a strain of Aerobacter aerogenes. A review of the literature has uncovered relatively few similar cases.

CASE REPORT

CASE 1. A fifty year old white male restaurant manager was admitted to Knickerbocker Hospital on July 30, 1957, because of intense pain across the base of the neck which extended to both shoulders and to the upper part of the arms.

He had been in excellent health throughout his life and had undergone a complete physical examination in February 1957. At that time his physician had prescribed a low calorie diet for obesity and slight hypertension. A roentgenogram of the chest, renal function studies, eye grounds and electrocardiogram were within normal limits; and the patient had no symptoms of illness whatsoever. Between February and June he felt perfectly well, and while adhering to the suggested diet slowly lost 15 pounds.

On June 16 severe and colicky pain developed suddenly in the left flank and radiated into the lower left quadrant and left inguinal region. The pain persisted for several hours and then disappeared. During the next week the patient had three similar recurrences; he was hospitalized elsewhere for diagnosis and treatment. An intravenous pyelogram showed the presence of a stone in the left ureter at the level of the ureteropelvic junction. Laboratory studies revealed a blood urea nitrogen of 18 mg./100 ml. and a serum uric acid of 7.5 mg./100 ml. No clinical or roentgenographic signs of gout could be found.

Cystoscopy was performed on June 29 after premedication which included Thorazine.® The urologist found the obstructing stone and maneuvered it back into the renal pelvis. The urine above the point of obstruction was grossly turbid but cultures surprisingly were negative. Two days after this procedure the patient had chills, fever and generalized abdominal pain. For the next few days he was extremely ill, and he became jaundiced as well as febrile and uremic. His temperature was septic in type and he continued to have brief shaking chills and diaphoresis. Laboratory findings included a blood urea nitrogen of 110 mg./100 ml., serum bilirubin 4.5 mg./100 ml., cephalin flocculation 3 plus, thymol turbidity 22 units, and alkaline phosphatase 4.5 Bodansky units. Urine culture was reported as negative. On treatment with penicillin and Terramycin,® his symptoms gradually improved, his temperature returned to normal, the jaundice cleared completely and the blood urea nitrogen dropped to 25 mg./100 ml.

At the height of his febrile illness the patient had complained of dull aching pain which he described as "boring through his back" in the interscapular area and spreading into the inner aspects of the upper part of both arms. At first, while the patient was acutely sick, little attention was paid to this complaint. However, although all other signs and symptoms subsided, the back pain persisted and steadily worsened. It was aggravated by movement of the neck or trunk, was constantly present regardless of position or posture,

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and was relatively unresponsive to the administration of analgesics. Roentgenograms of the chest and spine were taken but they did not reveal any abnormalities.

The patient declined to remain in the hospital for further observation and left one month after the onset of his difficulties. He was unable to return to work "because the pain was unendurable."

On July 20 the patient experienced a more excruciating pain over the lower posterior portion of his neck. This pain was constant and was made agonizingly worse by any motion of the neck, arms or trunk. At first it was felt in only the right shoulder and arm, but after a few days it was felt across both shoulders and down both arms to the elbows. The interscapular pain now seemed to have disappeared. Roentgenograms of the cervical spine were repeated and interpreted as showing a destructive lesion involving the fifth and sixth cervical spines. The patient was then referred to one of us and admitted to Knickerbocker Hospital for further diagnostic studies and therapy.

Careful review of the patient's history revealed no other significant features. He had never suffered any serious traumatic injuries or fractures. Except for the episode previously described, he had had no febrile illness of consequence since childhood. He specifically denied any knowledge of tuberculosis either in himself or among his friends or members of his family. There appeared to be no likelihood of exposure to unpasteurized milk or to the hides or furs of animals. The patient had never lived or travelled in any area of endemic mycotic infections. There was no history of arthritic symptoms or of familial occurrence of gout.

At the time of admission, physical examination revealed a slightly obese and well developed white man who appeared to be in severe distress. He was holding his neck rigidly in a fixed position and seemed to have extreme pain on any movement. The temperature was 100°F., the pulse rate was 72 and regular and the blood pressure was 140/70 mm. Hg. The head, eyes, ears, nose and throat appeared entirely normal. There was no scleral icterus. The lung fields were clear, and examination of the heart revealed no abnormalities. The abdomen was obese, soft, and there was no tenderness. No organs or masses were felt, and no tenderness was elicited at the costovertebral angle. On rectal examination, the prostate was normal in size and consistency, and free of nodules. The genitalia were normal. There was no lymphadenopathy, and the patient's skin was clear. The extremities presented no abnormalities, the neurologic examination revealed no disease of the cranial nerves, no sensory deficits, and no apparent loss of motor power. The deep tendon reflexes were symmetrically equal and active, and no pathologic reflexes were found. The patient had noted no paresthesias and displayed no evidence of cutaneous hyperesthesia. There was marked point tenderness over the fifth and sixth cervical spines, but no bony deformities, masses or skin changes were noted in this area. No other bone tenderness could be elicited. The deep muscles of the back in the cervicothoracic area were markedly spastic.

Roentgenograms of the cervical spine (Fig. 1) demonstrated destruction of the opposing surfaces of the fifth and sixth cervical spines, with erosion of both vertebral bodies, narrowing of the segmental interspace and anterior bulging of the prevertebral soft tissues. Calcium deposits were noted in several of the areas involved. There was kyphotic angulation of the lower cervical spine with the fifth and sixth vertebrae serving as the pivotal point. The appearance of the lesion was considered to be consistent with a spondylitic process of infectious etiology. Roentgenograms of the rest of the spine, the chest, skull, pelvis, ribs and scapulas showed no abnormalities.

The urine had a specific gravity of 1.012, was acid and contained a trace of protein, 6 to 10 white blood cells with 2 to 3 clumps per high power field and no erythrocytes. The blood non-protein nitrogen was 35 mg./100 ml., and the blood creatinine was 1.4 mg./100 ml. Aerobacter aerogenes grew on urine cultures taken on admission and again three weeks later. Blood cultures were negative on three occasions, and blood studies for febrile agglutinins were also negative. Tubercle bacilli could not be recovered on culture of the urine, and results of the first and second strength tuberculin skin tests were negative. The urine showed no Bence Jones protein. Aspiration of the bone marrow revealed only a slight increase in myeloid elements, mainly myelocytes, with no increase in plasma cells and no abnormal cellular elements. The serum electrophoretic pattern showed a minimal reduction in the albumin fraction but was otherwise within normal limits.

Examination of the peripheral blood exhibited a mild normocytic anemia: the hemoglobin was 9.6 gm./100 ml. and the red blood cell count was 3,450,000 per cu. mm. The total white blood cell count was 9,600 per cu. mm. with 71 per cent polymorphonuclear cells, 28 per cent lymphocytes and 1 per cent monocytes. The erythrocyte sedimentation rate was 78 mm./hour. Other determinations were reported as follows: serum uric acid, 5.7 mg./100 ml.; serum calcium, 9.6 mg./100 ml.; total protein, 6.2 gm./100 cc. with albumin value 3.1 gm./100 cc. and globulin value 3.1 gm./100 cc.; alkaline phosphatase, 3.2 Bodansky units; acid phosphatase, 0.9 Gutman units; the cephalin flocculation test was negative, and serum bilirubin was 0.2 mg./100 ml.

A roentgenogram of the abdomen showed a small calcific density at the lower pole of the left kidney. On intravenous pyelography the stone could be visualized in the lower renal pelvis. The kidneys and ureters were otherwise normal. Films of an upper gastrointestinal series and a barium colon enema offered no evidence of a lesion in the esophagus, stomach, small or large bowel.

It seemed most probable that the destructive bone changes represented an infectious osteomyelitic process. The sequence of events suggested that the urinary tract had been the original focus of bacterial infection, and that cystoscopic instrumentation had probably been the cause of hematogenous dissemination to the affected bony parts. On this assumption, and guided by sensitivity studies of the cultured A. aerogenes, Chloromycetin® 0.5 gm. and Furadantin® 0.1 gm. were administered four times a day.

In an attempt to verify this impression, and to exclude either neoplasm or some other infectious agent as a cause, a tissue diagnosis was sought by performing an aspiration biopsy. On August 7, under fluoroscopic control, an orthopedic surgeon introduced a needle directly into the lesion, using an anterolateral approach. No pus or other material could be aspirated. When the patient began to complain of pain in both wrists, it seemed prudent to attempt no further manipulation with the needle. A small amount of saline solution was injected into the area and then aspirated. This material was cultured on a variety of media, but no organisms (fungi, acid-fast bacilli, aerobic or anaerobic bacteria) could be grown. Microscopic examination of the smeared aspirate showed a few polymorphonuclear leukocytes and no atypical cells.

Cervical traction was applied after this procedure, and the patient experienced immediate relief of pain. Within three days he felt well enough to insist on being allowed out of bed, and with the aid of a metal collar and brace to insure stability, he began to ambulate very cautiously.

The results of this combined antibiotic and orthopedic management are best illustrated by the serial roentgenograms which were taken during the next three months. The film taken on August 23 (Fig. 2), two weeks after the application of traction, showed some correction of the gibbus-like angulation of the lower cervical segments with consequent widening of the space between the fifth and sixth cervical spines. These changes were undoubtedly due to the traction and did not seem to represent either progress or regression of the osteomyelitic process. However, by October 4 (Fig. 3) there was considerably more evidence of new bone formation and healing of the spondylitic lesions. The space between the fifth and sixth cervical spines appeared denser and narrower, indicating progress toward bony union. The last roentgenogram (Fig. 4) was taken on November 12, and clearly revealed a further stage of healing. More new bone had been deposited, the lesion appeared denser, and the space between the fifth and sixth cervical spine had been almost obliterated.

Clinical recovery began to be evident more quickly. As previously mentioned, when the cervical spine was stabilized in traction, the patient had no further symptoms of local or radicular pain. After he had begun to ambulate he experienced a returned sense of well-being and became noticeably more cheerful and optimistic. His appetite improved and he was able to sleep without sedation. The low grade fever subsided within three days after institution of antibiotic therapy and his temperature remained normal throughout the rest of his hospital course. Treatment with Chloromycetin and Furadantin was continued for the first ten days; then streptomycin 1 gm. each day and Achromycin® 250 mg. four times a day were substituted and given continuously for the next nine weeks. There was steady improvement of the patient's anemia and at the time of discharge his hemoglobin was reported as 12.6 gm./100 ml. This was a direct response to treatment of the underlying infection, and it occurred without the administration of any hematinics. The sedimentation rate decreased progressively and was 26 mm./hour just before the patient went home.

The patient was followed at regular intervals after discharge. He remained entirely asymptomatic. Cervical traction was stopped but he continued to use a neck brace during the day. Over a period of four weeks this was gradually discontinued without any untoward consequences. Careful follow-up roentgenograms of the cervical spine, taken at biweekly intervals, showed progressive bony union of the fifth and sixth cervical vertebrae. The patient felt and looked well. Unfortunately, he regained all his lost weight and more with a return of his appetite.

On January 8 he was examined by a urological consultant. An intravenous pyelogram revealed persistent evidence of a small stone in the lower pole of the left kidney. The dye was well concentrated. The patient had microscopic pyuria which persisted to the time of writing. Urine culture once again revealed the presence of A. aerogenes. Gantrisin® was administered over a period of four weeks; a repeat urine culture was sterile. Surgical intervention to remove the calculus was not advised.

The patient has lost about 15 degrees of cervical hyperextension, but there is no other functional impairment of his spine. He is once again on a low calorie reducing diet.

Comment: This patient was admitted to the hospital because of excruciating radicular pain. He had been well until six weeks previously when left ureteral colic developed. Intravenous pyelography demonstrated a calcified stone obstructing the uteropelvic junction; cystoscopy was subsequently performed. Although urine from above the point of obstruction was grossly turbid, culture of this material was reported as sterile. Soon after this manipulative procedure the patient became seriously ill with obvious sepsis; penicillin and Terramycin were administered. Azotemia and jaundice developed, but

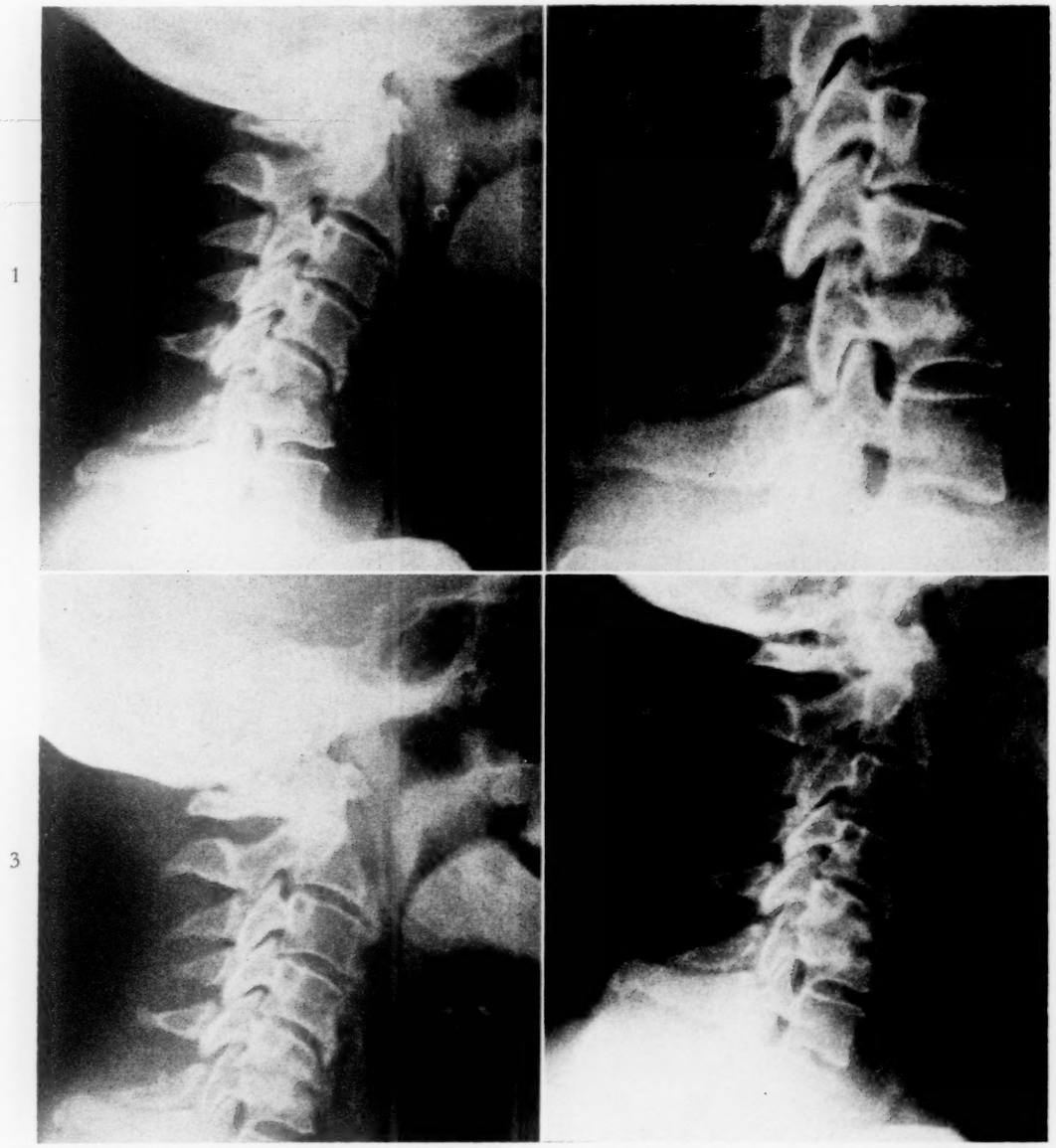


Fig. 1. Case 1. Destruction of the opposing surfaces of the fifth and sixth cervical spines, and erosion of the vertebral bodies. The interspace is narrowed and there is kyphotic angulation of the lower cervical spine. Areas of bone regeneration are already apparent.

Fig. 2. Widening of the interspace and partial correction of kyphotic deformity, subsequent to cervical traction.

Fig. 3. Significant healing has occurred with evidence of early fusion of the fifth and sixth cervical spines.

Fig. 4. Almost complete ankylosis of the fifth and sixth cervical spines has occurred.

subsided in a matter of days. With improvement, a dull, aching persistent pain developed in the interscapular area. This increased in severity and subsequently became localized more sharply in the lower cervical spine. A roentgenogram of this region was reported as being within normal limits. The patient left the hospital, and over the next two weeks his condition deteriorated. A second roentgenographic study demonstrated destruction of the fifth and sixth cervical vertebrae.

Physical examination after transfer revealed marked limitation of motion of the neck, considerable spasm of the contiguous muscle

groups, and point tenderness over the spinous processes of the lower cervical vertebrae. The previously reported positive roentgenographic findings were confirmed. A urine culture was overgrown with A. aerogenes. An exhaustive workup was otherwise completely normal.

Under direct fluoroscopic control, a needle was inserted into the cervical lesion. Direct aspiration was unproductive; saline solution was instilled locally, aspirated, and cultured with negative results. An attempt at biopsy of the involved vertebrae was unsuccessful.

Thereafter the patient was treated by cervical traction and antibiotics, with dramatic results. Symptomatic remission was rapid and complete. Serial roentgenograms demonstrated a striking healing response. The patient was discharged from the hospital with partial fusion of the vertebral segments; the process was completed subsequently.

CASE II. A sixty-nine year old white man entered University Hospital on September 7, 1955, because of symptoms of uncontrolled diabetes for the previous two weeks. His diabetes had been discovered during a routine screening examination twelve years earlier. Until the present illness began the disease had been clinically asymptomatic. The patient had never taken insulin and had maintained good control of his diabetes by adhering to a standardized diet.

Three weeks before admission a pustular infection developed in the left nostril which became swollen and painful. An otolaryngologist treated this with antibiotics and hot wet dressings, and there was relief of the local pain and inflammation. Subsequently the patient noticed increased thirst, urinary frequency, loss of appetite, fatigue and a constant feeling of drowsiness. In a two-week period he lost 10 pounds; marked polydipsia and polyuria developed, and he was becoming quite lethargic. An internist examined the patient at this time and noted obvious indications of mental disturbance and dehydration. He found that the urine contained 3 plus sugar and 2 plus acetone. Unable to find any ready explanation for the changed diabetic condition, he urged that the patient be hospitalized for further study and treatment.

Physical examination on admission disclosed an elderly white man who was slightly dehydrated and mentally torpid. The temperature was 101°F., the pulse rate 80 and regular, and the blood pressure 130/80 mm. Hg. A small, pink, partially healed furuncle protruded from the wall of the left nostril. The tongue appeared smooth and red, but the pharynx was clear. The head and neck were otherwise within normal limits. Funduscopy showed grade 1 arteriosclerotic changes without evidence of diabetic retinopathy. The lungs were clear, and examination of the heart revealed no abnormalities. The abdomen was soft; no tenderness was noted and no organs or masses were felt. The prostate was moderately enlarged, smooth and firm. The genitalia were normal. The extremities were essentially normal. There was no generalized lymphadenopathy, and the skin was clear. Results of the neurologic examination were completely normal.

Laboratory data were as follows: hemoglobin 10.6 gm./100 ml.; red blood cell count, 3,950,000/cu. mm.; white blood cell count, 13,600/cu. mm., with 78 per cent polymorphonuclear cells. The urine showed a specific gravity of 1.010, contained a faint trace of protein, and was strongly positive for both sugar and acetone. Four to five red blood cells, innumerable white blood cells, and many bacteria were reported on microscopic examination. The sedimentation rate was 120 mm./hour, the blood urea nitrogen 28 mg./100 ml., the serum creatinine 1.4 mg./100 ml., and the fasting blood sugar 230 mg./100 ml. Hemolytic coagulase-positive Staphylococcus aureus was recovered from culture of the urine. An intravenous pyelogram showed good excretion of the dye bilaterally, and normal calyces and ureters were visualized.

At this point it appeared that an uncomplicated infection of the urinary tract adequately explained the patient's loss of diabetic control. Treatment was begun with Achromycin 2 gm. each day and the temperature quickly returned to normal. On 35 units of NPH insulin every day, the glycosuria was reduced to trace amounts. However, the patient did not feel well despite the disappearance of fever, and he continued to need 25 to 35 units of NPH insulin daily.

On September 17 he began to complain of pain over the area of the lumbosacral spine, localized more specifically to the right side, radiating outward to the right iliac region and downward toward the right hip. No skeletal, muscular or skin changes could be found and there were no abnormal neurological signs. During the next few days the pain grew more intense, and became constant irrespective of position.

A roentgenogram of the lumbosacral spine and pelvis was described as showing marked narrowing of the interspace between the first and second lumbar vertebrae, with advanced localized hypertrophic changes. Since the urine was now free of protein and showed only occasional white blood cells, the administration of Achromycin was discontinued and the patient was given aspirin, grains XV, four times a day on the assumption that his pain was arthritic. A four day trial with salicylate afforded the patient no relief whatsoever, and the medication had to be stopped because he began vomiting. The patient then reported that the back pain had shifted its location and was situated most prominently on the left side of the lumbosacral spine.

Less than a week after antibiotic therapy was terminated the temperature again rose and began to

present a pattern of irregular, low grade elevations to about 100°F. Diaphoresis occurred during the night and early morning hours, and the patient complained of anorexia and malaise in addition to constant bone pain. Tachycardia of 100 to 110 was persistently present, and there were frequent premature beats. The sedimentation rate was now 126 mm./hour and a blood count showed persistence of the mild anemia with a white blood cell count of 8,900 per cu. mm. and a slight shift to the left. Roentgenograms of the lumbar spine again were said to reveal only hypertrophic osteoarthritic changes and narrowing of the space between the first and second lumbar vertebrae.

The presence of an occult neoplasm or lymphoma was now seriously considered, and for the next two weeks the patient underwent further diagnostic studies. Bone marrow aspiration revealed a picture of normal cellularity, remarkable only for a mild granulocytic hyperplasia. The urine was negative for Bence Jones protein. The total serum protein was 7 gm. with 3.6 gm. albumin and 3.4 gm. globulin. The serum acid phosphatase was 1.6 Gutman units, the alkaline phosphatase 2.6 Bodansky units, serum uric acid 3.2 mg./100 ml., and a repeat blood urea nitrogen was within normal limits. The stools were consistently negative for occult blood. Blood cultures showed no growth. Another roentgenogram of the lumbosacral spine was read as essentially similar to the first two.

During this period there was little change in the patient's clinical course. He remained febrile, complained of weakness and suffered almost continuous intractable back pain. He became very depressed, emotionally withdrawn, and showed no interest in leaving his bed.

On October 12 a fourth roentgenogram was taken of the lumbosacral spine. (Fig. 5.) This was compared with the previous films and was reported as showing progressive destruction of the adjacent articular surfaces of the bodies of the first and second lumbar vertebrae, narrowing of the segmental interspace and a moderate gibbous deformity. The radiologist now believed (in retrospect) that he could detect a small area of bone erosion at the left inferior margin of the body of the first lumbar vertebra on the immediately previous roentgenogram. On October 13, as if by coincidence, the laboratory reported that a blood culture was positive and identified the organism as hemolytic Staph. aureus, coagulase-positive. *In vitro* studies showed this organism to be sensitive to penicillin, Gantrisin and a number of broad-spectrum antibiotics—exactly the same spectrum of sensitivity as that displayed by the staphylococcus previously recovered from the patient's urine. Supplementary roentgenographic studies during the next two weeks showed further destructive changes of the two involved vertebral bodies with erosion of the bridging hypertrophic excrescences. Slight bulging of the psoas outline on each side was also noted.

On November 1 aspiration biopsy of the second lumbar vertebral body was carried out under fluoroscopic control. The needle was introduced into the vertebra without difficulty and two specimens of bone were obtained. The pathologic report was as follows: "Section shows a piece of normal appearing cartilage, fibrous connective tissue and cancellous bone and marrow. The fibrous connective tissue, which in some areas appears compressed, contains an infiltrate of inflammatory cells consisting of polymorphonuclear leukocytes and plasma cells. The trabeculae of bone show no unusual changes except for prominence of osteoblasts in some areas. The associated marrow shows some fibrosis and has an inflammatory infiltrate consisting of polymorphonuclear cells, lymphocytes, eosinophiles and plasma cells. The blood clot is largely made up of erythrocytes and scattered leukocytes. Diagnosis: chronic osteomyelitis of body of lumbar spine."

Hemolytic coagulase-positive Staph. aureus, grew on cultures of the aspirate which showed *in vitro* sensitivities comparable to its fellow organisms from the urine and peripheral blood. Cultures for brucella and tubercle bacilli were later reported as negative, and a guinea pig inoculated with the biopsy material showed no sign of tuberculosis at autopsy.

Therapy consisted of the daily administration of Achromycin 2 gm., penicillin 1,200,000 units and Mycostatin® 500,000 units. An orthopedic consultation was obtained to evaluate the actual and potential problems created by the mechanical damage to the patient's spine. It was decided to keep the patient in a recumbent position during the early phases of healing; i.e., to eliminate pressure along the longitudinal axis of the vertebral column and thus avoid the dangers of further vertebral collapse and possible cord compression.

Within twelve days of the institution of antibiotic therapy, the temperature gradually returned to normal and subsequently remained normal. The back pain also diminished gradually and after about three weeks was no longer noticeable. After approximately a week of treatment the patient said he felt much better, and he showed definite objective improvement in appearance, appetite and renewed interest in his surroundings. The daily requirement of insulin decreased steadily and after six weeks the diabetes was controlled sufficiently to permit the discontinuance of insulin therapy.

Laboratory studies confirmed the clinical impression of steady improvement. The sedimentation rate was 136 mm./hour when full scale antibiotic treatment was started. At the end of a month it had dropped to 57 mm./hour and a month later it had fallen to 18 mm./hour. No specific measures (such as transfusions or iron therapy) were utilized to correct the patient's anemia. However, after adequate treatment of the infection responsible for the anemia there was a steady rise in the patient's hemoglobin and erythro-

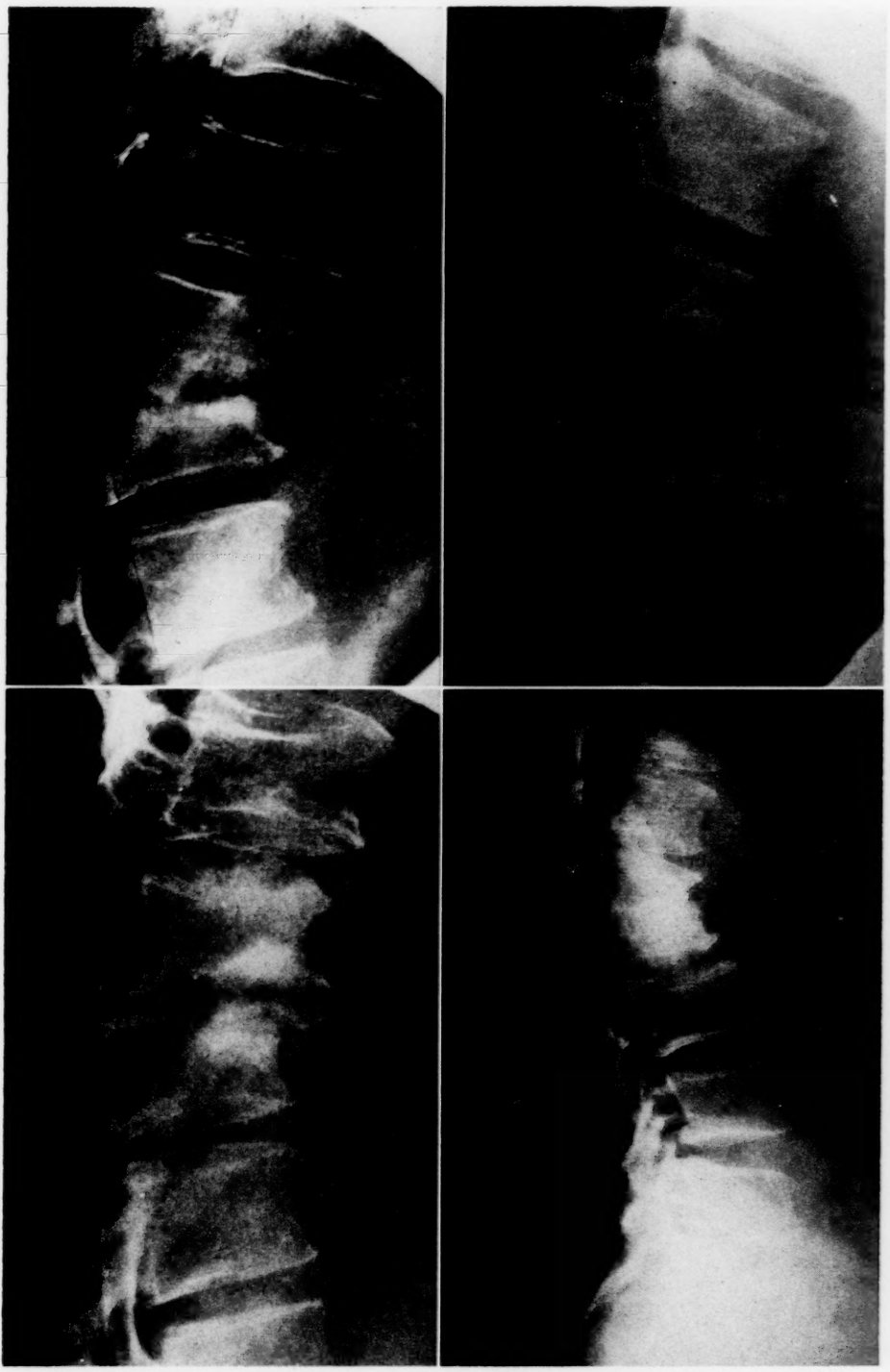


FIG. 5. Case II. Destruction of adjacent articular surfaces of the first and second lumbar vertebrae, narrowing of the segmental interspace and moderate gibbous deformity. Early evidence of calcium deposition anterior to the involved vertebrae is seen.

FIG. 6. Continued evidence of bone destruction and calcium deposition with some correction of the kyphosis.

FIG. 7. Significant healing has occurred with the development of early ankylosis; marginal bony bridges are conspicuous.

FIG. 8 Complete bony union of the first and second lumbar vertebrae has occurred.

cyte count. At the beginning of chemotherapy the hemoglobin had been reported as 9.2 gm./100 ml. and the red blood cell count 4,150,000 per cu. mm. By December 7 the hemoglobin was 12.2 gm./100 ml. and red blood cell count 4,640,000 per cu. mm. On January 5, shortly before discharge, the hemoglobin was 13.2 gm./100 ml. and the red blood cell count 4,870,000 per cu. mm.

The slow progress toward healing of the bony lesions is indicated in the accompanying illustrations. Figure 5 demonstrates the destructive process as it appeared before treatment. After two weeks of therapy (Fig. 6) there was no particular change in the osseous lesions but there was some correction of the spinal angulation. On December 14, there was considerable evidence of healing with new bone formation in the areas adjacent to the articular surfaces of L_1 and L_2. (Fig. 7.) By January 9, a more advanced stage of healing had taken place (Fig. 8); there was evidence of further formation of bone and almost complete obliteration by bony ankylosis of the intervertebral space.

Antibiotic therapy was continued until the beginning of December, for a total of seven consecutive weeks. Near the end of December the patient was allowed to sit up in bed wearing a specially fitted orthopedic belt and back brace. By the middle of January he was able to stand and begin walking, still wearing the brace for support. He made rapid and enthusiastic progress in ambulation and was able to leave the hospital on February 7, 1956.

Despite this generally favorable course several complications were encountered. Because of the prolonged period of bed rest in a supine position, decubital ulcers developed; they were distressingly painful and posed the twin threats of recurrent infection and disturbance of diabetic balance. This problem required exceptionally vigorous nursing care and fortunately did not become serious.

The other complications were of an even more serious variety. During the second week of November fecal incontinence developed and persisted until almost the end of the patient's hospital stay. In December it was noted that the Babinski sign had become positive on the right side. No other neurological changes appeared, but it seemed most likely that the loss of bowel control and the abnormal extensor response were due directly to involvement of the cord by compression of the diseased lumbar vertebrae. Fortunately, no permanent neurologic damage occurred.

Comment: Exacerbated symptoms of diabetes mellitus developed in an elderly man because of an infection of the urinary tract with hemolytic Staph. aureus. Although he was treated with large doses of Achromycin and underwent no urological instrumentation, he continued to be febrile. After about ten days, he began to complain of low back pain. The pain and fever persisted throughout the next month, during which time three roentgenograms of the spine were read as being within normal limits.

Four weeks after the onset of back pain there was radiologic evidence of a lytic spinal lesion for the first time, and a blood culture was positive for hemolytic Staph. aureus. Needle biopsy of the involved vertebrae confirmed the diagnosis of osteomyelitis, and hemolytic Staph. aureus grew on cultures of the aspirated material.

The patient responded well to antibiotic and conservative orthopedic therapy, and serial x-ray films showed slow but progressive healing of the bony lesions. He recovered fully after four months of treatment.

CLINICAL PICTURE

Osteomyelitis of the spine is a rather uncommon condition. Its incidence, in large groups of patients with all forms of osteomyelitis, was reported by Hahn [*6*] in 1895 as 0.2 per cent, by Wilensky [*7*] in 1929 as 1.5 per cent and by Kulowski [*8*] in 1936 as 3.9 per cent. It is probable that this rising prevalence is due more to better diagnostic technics and greater awareness than to any true statistical increase.

Makins and Abbott [*9*] (1896) found that the average age of their patients was fourteen years. Forty years later Kulowski found the average age of 102 patients to be thirty-one years. The latter figure is consistent with those given in more recent series [*10–12*], in which the peak incidence was in the third and fourth decades. It is more common in males, an average ratio of 3 to 1 being reported in the larger series of cases.

In the largest number of patients, lesions developed in one or more of the lumbar vertebrae. Involvement of the thoracic spine follows next in frequency, and the cervical spine is least often affected; multiple areas of vertebral involvement have also been reported.

The clinical picture of vertebral osteomyelitis may be highly variable, and a number of attempts have been made to distinguish acute, subacute and chronic forms as distinctly different syndromes [*8,13,14*]. Thus, especially in the older literature, and occasionally today, there are accounts of patients who suddenly became ill with hyperpyrexia, chills, weakness, prostration and other obvious signs of overwhelming sepsis in addition to localized bone pain, the disease running a rapid and fulminating course. The local symptoms due to spinal

osteomyelitis are usually completely overshadowed. In other cases the toxemia may be slight and although the signs of an inflammatory process are present these may be too generalized and mild to draw attention to any focus of infection and are not nearly as prominent as the particular complaint of pain in the spine. At the far end of this spectrum, a considerable number of so-called chronic cases have been reported in which there was no overt evidence of sepsis at the time the patients began to have symptoms referable to lesions in bone. In almost all these cases, however, there was a previous febrile episode associated with infection either of the genitourinary tract or of the skin. The period of bacteremia may antedate by many months the symptoms of focal osteomyelitis.

The two cases presented here exemplify the courses and the major clinical features that characterize the moderately acute form of vertebral osteomyelitis. In each instance there was a discrete focus of initial infection, manifest bacteremia, and subsequent spinal complaints that were localized.

The most common and constant symptom of osteomyelitis is pain, often diffuse at the onset but becoming severe and more precisely localized to the involved vertebrae as the disease progresses. The pain is usually continuous thereafter, confined to a definite area, present without regard to the patient's position, and made much worse by standing or by any motion of the spine. When severe, the pain may be intractable, even the administration of narcotics failing to relieve it completely.

If the disease progresses further, there may be symptoms related to extension or complication [*8,10,12,13,16,17*]. These include local extension to the adjacent retropharyngeal, retroesophageal, mediastinal, pleural, pericardial or retroperitoneal structures, wider dissemination to the dura or the meninges, and the complications that follow destruction of the bony spine in the form of damage to the cord.

The laboratory findings, apart from specific bacteriology, are not, as a rule, of any definitive significance and are what one would expect in the presence of any significant infection.

PATHOGENESIS

Osteomyelitis of the spine may develop in a variety of clinical situations. Among these, direct trauma or surgery as a source of infection is probably the most obvious [*8*]. At least one case has been attributed to lumbar puncture [*10*]. However, in the majority of cases the infection is embolic in nature. As one reviews the literature referring to the problem of septicemia in relation to the primary seeding portal of entry, one is impressed with the importance of the genitourinary tract as the source of infection [*18*]. In 1931 Carson [*19*] reported four patients with vertebral osteomyelitis, staphylococcal septicemia and infection of the urinary tract. He made no attempt to correlate these facts, admitting that "the determination of the lesion to the bodies of the vertebrae is very difficult to explain." In 1934 Selig [*20*] reported a case of osteomyelitis of the spine complicating cystoscopy. In 1935, Kretschmer and Ockuly [*21*] reported three instances of osteomyelitis following surgery of the urinary tract. Kusonoki [*22*] next reported six cases of osteomyelitis following infection of the urinary tract; in three of these there was involvement of the spine. The association of infection of the urinary tract and spinal osteomyelitis was definitely discussed by Deming and Zaff [*23*] (1942) who correlated their findings with the work of Batson in incriminating the vertebral venous plexus as the route of the spread. Donahue [*24*] reported two cases of spinal osteomyelitis following prostatic surgery. Hurwitz [*17*], and Adlerman and Duff [*25*] described interesting cases of cervical osteomyelitis, one complicated by a retroesophageal abscess. In 1954, Mussey [*26*] described two cases of spinal osteomyelitis subsequent to urological instrumentation. De Feo [*27*] described two cases occurring in patients following prostatectomy in 1954. An excellent article by Leigh [*28*], who presented nine cases, was published the following year. In seven of these cases, either surgery or manipulative procedures of the urinary tract preceded the development of vertebral osteomyelitis. Henson and Coventry [*12*] in 1956 reviewed the subject of vertebral osteomyelitis and described the experience with it at the Mayo Clinic, reporting seven additional cases; in five cases the diagnosis was confirmed by needle biopsy. Liming and Youngs [*29*], Lame [*30*], and recently Silverthorne [*31*] have reported additional cases.

The pointed query posed by Carson [*19*], underscoring the oddity of spinal localization following systemic infection, might still remain unanswered today were it not for the important research on the vertebral venous plexus first published by Batson [*32,33*]. By applying his

laboratory observations to the patient, he was able to explain for the first time on an anatomical basis, the mechanism of so-called paradoxical metastases in prostatic carcinoma. Using the same reasoning, paradoxical metastases of a variety of other agents, including air or bacteria, can likewise be better understood. This would clearly explain the occurrence and distribution of embolic osteomyelitis of the vertebrae as a sequela to infection of the genitourinary tract. Simultaneous involvement of multiple areas of the vertebral column would likewise be understandable. Therefore, the recent increase in the incidence of septicemia arising from an initial focus in the genitourinary tract and the modest increase in the number of cases of spinal osteomyelitis occurring as a complication of this infection is not surprising. This can occur without instrumentation or manipulation, as shown by our second case. However, the majority occur as a complication of instrumentation, manipulation or surgery as in our initial case.

A variety of causative organisms have been reported in osteomyelitis affecting the vertebrae. Until 1946 approximately 70 per cent of all cases were caused by strains of staphylococci. Today, although infection by staphylococcal organisms remains the largest group in terms of numbers, the proportion is less impressive because of the increased incidence of infections of the urinary tract due to enteric bacilli. As a result of the recent emergence of resistant strains of these groups of organisms it would appear reasonable to predict that the number and severity of cases of embolic osteomyelitis of the spine arising from a genitourinary focus will increase appreciably.

The development of focal abscesses in the spinal bodies is favored by the voluminous yet sluggish flow of blood through the vertebral venous plexus [*8*]. The lesions begin as discrete foci of carious necrosis which tend to spread rapidly, involving the vertebral bodies, neural arches, transverse and posterior processes, and the intervertebral discs. It is a hallmark of the disease that two contiguous vertebral segments and the intervening disc are almost invariably involved, with partial or total destruction [*8,12,34*]. This tendency to spread from one vertebral body to the next is one of the most important points in differentiating the pyogenic from the tuberculous form of vertebral osteomyelitis.

An equally distinguishing feature of pyogenic osteomyelitis is that proliferative repair, healing and the formation of dense new bone occur early and proceed with vigor [*8,12,13*]. The radiologic picture invariably shows the stages of breakdown and repair occurring simultaneously. Through the formation of bony bridges and thick sclerotic replacement of previously destroyed tissue, full healing with ankylosis often occurs.

Complications of vertebral osteomyelitis depend in part on the location of the spinal lesions. From a focus in any of the posterior spinous processes, a superficial skin abscess may develop. Much more commonly, the initial lesion is in the vertebral body itself, and spreads anteriorly to involve the prevertebral space. This may lead to a retropharyngeal or retroesophageal abscess at the cervical level. At the thoracic level, a retromediastinal abscess may arise and, extending further, may jeopardize the pericardium or pleura. Lesions in the lumbar spine may cause an infection of the retroperitoneal space even more frequently.

If the osteomyelitic focus lies in the posterior portion of the vertebral body, it may penetrate the relatively weak posterior longitudinal ligament and burrow directly into the spinal canal with the formation of an extradural abscess. Should the dura be perforated, the obvious consequence is a purulent meningitis.

Vascular complications include thrombosis of the vertebral veins, arterial thrombosis with infarction of the spinal cord and an occasional mycotic arterial aneurysm [*8*].

Damage to the spinal cord is encountered as a serious and sometimes fatal complication of subluxation of a vertebral segment.

ROENTGENOLOGIC FEATURES

The problems of the roentgenographic diagnosis of vertebral osteomyelitis have drawn the attention of many investigators [*8,11,13,34,35*]. Most radiologists are now in accord that reliable diagnostic criteria are few. However, there are a number of points which may be helpful even on single films. Apart from these, there is the most important point of all; serial films taken during the course of the disease will establish the diagnosis of osteomyelitis and eventually differentiate the pyogenic from the tuberculous form.

The first difficulty in establishing the diagnosis roentgenographically is often that of finding any lesion at all. Invariably there is a time lag between the beginning of symptoms and the

appearance of the earliest roentgenographic changes. This delay of anywhere from two or three weeks to several months may frustrate and delude the clinician. Persistent repetition of x-ray films is therefore necessary if there is a justifiable suspicion of bone disease. Involvement of multiple segments of the spinal column is not uncommon. It is important, therefore, that an entire bone survey be made. Spot and oblique views should be taken at levels which are particularly suspect, and tomograms utilized to explore fully all dimensions of the spine and surrounding soft tissues.

The earliest roentgenographic changes appear as circumscribed areas of decreased bone density close to the epiphyseal ring or cartilagenous plate which imparts a peculiar fuzziness to the borders of the vertebral body. At the same time, narrowing of the intervertebral space may be seen paralleling the destruction of the intervertebral disc. Later, the areas of bone destruction become larger and more ragged in appearance, and adjacent vertebral borders have an irregular chewed-out appearance. Involvement of two or more adjoining vertebral bodies with at least partial loss of the intervertebral disc and its space is a rather constant finding. Frequently destruction is extensive enough to cause partial or complete vertebral body collapse with angulation of the spine.

Manifestations of bone regeneration and healing are extremely important confirmatory diagnostic findings and are, of course, helpful in guiding the clinical management of the patient. In pyogenic osteomyelitis, roentgenographic evidence of new bone formation becomes apparent almost simultaneously with the development of lesions. The earliest indication of this process is the appearance of small ossification centers in or around the margins of destroyed bone. They slowly extend, bridging the area of destruction. When the process is completed, ankylosis will have occurred.

A number of the features just described are helpful in differentiating pyogenic osteomyelitis from neoplasms of the spine. The latter are not associated with regenerative repair, are almost invariably limited to the vertebral body and its bony appendages and do not, as a rule, invade the disc or traverse the intervertebral space. Despite these clearly indicated differences, it should be borne in mind that in any single instance the lytic lesions produced by these two processes may be indistinguishable; the eventual roentgenological diagnosis often depending upon a series of films.

Likewise, the roentgenologic differentiation of pyogenic and tuberculous vertebral osteomyelitis may be exceptionally difficult. Most, if not all, of the valid criteria depend on observations which can only be gleaned from an adequate series of films. Pyogenic osteomyelitis is a more rapidly destructive disease, producing its damage in a matter of weeks [*36,37*]. The much slower tuberculous process generally progresses much farther in terms of final damage, often producing total disintegration of vertebrae and complete collapse of spinal segments; pyogenic osteomyelitis rarely causes either of these findings. Tuberculous osteomyelitis, like neoplasms, does not typically cross the intervertebral space and does not share the predilection for the intervertebral disc. The processes of new bone formation and healing by proliferation and ankylosis are unique to pyogenic osteomyelitis.

When roentgenograms do permit accurate localization of the lesion, needle biopsy should be performed to confirm the nature of the underlying pathologic condition. The procedure was first reported by Ball [*38*] in 1934, and the best technic was described in detail by Valls et al. in 1948 [*39*]. Fluid and exudative material or plugs of tissue, or both, can be removed for study by this method, using a serrated biopsy needle [*40*]. Fluoroscopic control of needle placement is mandatory in every instance. Biopsy of the cervical vertebrae is especially difficult and hazardous. The prior institution of antibiotic therapy is an important factor influencing bacteriologic confirmation at the time of aspiration, as in our first case. In our second case, local biopsy was confirmatory and the same organism grew on culture of the aspirate, with the same antibiotic sensitivities as those previously grown out of blood and urine. The histologic appearance of biopsy material may occasionally be misleading, and if so, final confirmation must await bacteriologic culture. Therefore, whenever possible, both biopsy specimen and cultures should be obtained. In the absence of positive bacteriologic or biopsy confirmation, the diagnosis is presumptive and must be made on the basis of the evolutionary clinical picture, the roentgenological features, and the therapeutic response.

Differential diagnosis, in addition to the more common pyogenic infections, includes tuberculosis, brucellosis, fungal and salmonella infections. Multiple myeloma, metastatic car-

cinoma and other neoplastic lesions must also be considered.

TREATMENT

The important features of therapy include eradication of the specific invading bacterial pathogen, local therapy of the spine, and prevention and treatment of complications. The use of antibiotics with any element of nephrotoxicity should be avoided whenever possible because of the high incidence of underlying renal disease often found in these patients. The local treatment of spinal osteomyelitis is likewise of extreme importance if irreversible damage to the spinal cord is to be avoided. The usual program will include splinting of the spinal column with a brace, a plaster cast or a corset until roentgenographic evidence of healing is manifest. Traction will often be of great help in relieving radicular pain, which can be severe. As healing occurs, mobilization in graduated stages is permitted. If the response to antibiotic therapy is favorable, the earliest roentgenographic evidence of fusion of the involved vertebrae will become visible in approximately six weeks, and be completed in three to six months. Once fusion has occurred, the disease is permanently cured. The management of complications is of great importance. In the case of spinal cord complications, prevention is of the essence. For that reason, early diagnosis and the institution of proper therapy as expeditiously as possible is imperative.

SUMMARY AND CONCLUSIONS

Embolic osteomyelitis of the spine is an uncommon entity with a rather typical evolutionary clinical pattern. Persistent back pain, progressive in character and otherwise unexplained, developing subsequent to septicemia, should arouse suspicion.

The genitourinary tract must be regarded as the most important portal of entry responsible for initiating and seeding the infection. The more common bacterial invaders disseminating from this focus are the staphylococcal and enteric bacillary groups.

A normal roentgenogram of the spine should be anticipated early in the course of the disease and serial films are needed to demonstrate the process of vertebral and disc destruction from its inception. Roentgenologic evidence of repair becomes manifest almost simultaneously. Tomograms may be an important aid in delineating the characteristic lesions. Needle biopsy, when properly performed, is a safe and extremely valuable aid in establishing the diagnosis.

The earliest institution of correct and specific antibiotic and orthopedic therapy can shorten the otherwise protracted clinical course and can prevent serious complications.

ADDENDUM

Since this article was accepted for publication, another interesting case has been observed.

CASE III. On June 5, 1959, a sixty-two year old white man was admitted to Knickerbocker Hospital with an acute febrile illness accompanied by restlessness and altered sensorium.

The history obtained on admission was necessarily fragmentary because of the patient's obtunded state, and only later could adequate information be obtained.

Four days prior to admission, symptoms and signs of urinary retention developed. The patient had had a syphilitic infection many years previously which was treated with arsenicals and penicillin. The disease progressed, however, tabes becoming manifest along with symptoms of a "cord bladder" for which he was hospitalized with acute urinary retention four years previously in another institution. From October 1958 until his admission to Knickerbocker Hospital, he received prostatic massage at biweekly intervals.

Physical examination on admission revealed an acutely ill and somewhat confused subject with a temperature of 105°F. A few rales and decreased breath sounds were noted at the base of the right lung. Evidence of syphilitic involvement of the central nervous system was corroborated by the findings of Argyll-Robertson pupils, absence of deep tendon reflexes and position sense in both lower extremities, and absence of deep pain sensation. There was no rigidity nor other signs of meningeal irritation. The prostate was not enlarged, but a residual urine of 600 cc. was obtained. A tentative diagnosis of urinary retention with infection and pneumonitis was entertained. On the second hospital day, because of persistence of mental confusion and fever, a spinal tap was performed. The fluid was noted to be thick and turbid; there was a striking pleocytosis, largely polymorphonuclear in type, increased protein and decreased glucose and chloride. There was also evidence of a subarachnoid block. Gram stain of the spinal fluid revealed innumerable gram positive cocci. Culture of the material grew out hemolytic Staph. aureus, coagulase positive. The same organism was cultured from the patient's blood and urine.

Vigorous antibiotic therapy was instituted with penicillin, streptomycin, Chloromycetin and later, erythromycin. The temperature, which remained elevated during the first two days, decreased thereafter.

On the eleventh hospital day, kanamycin was added to this therapy.

Intrathecal enzymes (pancreatic dornase, 1 million units per dose) were given daily for seven days following the initial spinal tap along with other supportive measures. Twelve hours subsequent to the initial administration of intrathecal enzymes, nuchal rigidity first appeared.

It was believed that the original focus of infection in this case was localized in the urinary tract. Subsequent either to prostatic massage or urinary retention there was dissemination of pathogens into the blood stream with consequent vertebral embolization and osteomyelitis. This was further complicated by formation of a paravertebral abscess with localized extension into the subarachnoid space. When enzymes were administered intrathecally, the localized subarachnoid infection disseminated widely, producing the classic manifestations of meningitis.

This interpretation of events was confirmed by roentgenograms which demonstrated the characteristic findings of osteomyelitis involving the third and fourth lumbar vertebrae.

A needle biopsy of the involved vertebrae substantiated this diagnosis by revealing evidence of bone necrosis with sequestrum formation. A culture of the aspirate grew out Staph. aureus, coagulase positive.

The clinical course was favorable. By the sixteenth hospital day the patient's sensorium was clear and there was no evidence of nuchal rigidity. The temperature gradually decreased, becoming normal approximately one month after admission. During the next eight weeks the patient completed an uneventful recovery and was discharged from the hospital.

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Fusobacterium Septicemia

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SEPTICEMIA with anaerobic organisms is being reported with increasing frequency since the use in hospital laboratories of appropriate culture methods has become more prevalent. The most frequently isolated species belong to the genera streptococcus, clostridium and bacteroides [*1*]. Less often seen is fusobacterium, a genus of non-sporulating, gram-negative, anaerobic and rod-shaped organisms found characteristically on the mucous membranes of the mouth and genitalia and in the alimentary tract of mammals [*2*]. Numerous reports, reviewed in monographs by D. T. Smith [*3*] and Bøe [*4*] have incriminated fusobacterium either alone or associated with spirochetes and other microorganisms in cases of appendicitis, liver abscess, gangrene of the lung, empyema, sinusitis, otitis, pharyngitis, balanitis, endometritis, cellulitis and noma. Less frequently fusobacteria cause septicemia and metastatic abscesses. Only five previously reported cases of septicemia have been culturally proved [*5–8*].

The present report describes a case of fusobacterium septicemia corroborated by four positive blood cultures and one positive bone marrow culture.

CASE REPORT

A forty-six year old white man, a telephone repair supervisor from Washington, D. C., was in excellent health until November 1957, when, ten days after a hunting trip to Maine, he had the sudden onset of fever with elevations in temperature to 104°F., shaking chills and profuse diaphoresis. During the trip he had camped in the open, drunk from mountain streams, and skinned an owl. The chills, fever and sweats continued daily for six weeks despite frequent intake of aspirin. He became anoretic and lost approximately 25 pounds. The stools appeared to be normal, but the urine was darker than usual. He was admitted to the Arlington Community Hospital on January 17, 1958, where he was afebrile the first three days; however, for the next four days he had intermittent temperature elevations to 104.5°F. From the seventh to the thirteenth hospital day, chloramphenicol (2 gm./day) was given, but because of minimal response a combination of penicillin (1,200,000 units/day), dihydrostreptomycin (1.5 gm./day) and chlortetracycline (1 gm./day) was substituted. After two days of this therapy he became afebrile, and antibiotic therapy was discontinued on the twenty-second hospital day.

Laboratory studies during this hospitalization showed leukocyte counts of 9,600 and 8,800/cu. mm. with normal differentials. The results of hemoglobin, alkaline phosphatase and bromsulphalein tests were normal. Three blood cultures taken January 17, 20 and 22 were sterile. Thioglycollate medium was used and the cultures were incubated for fourteen days. One bone marrow culture for bacteria, including brucella, was negative. Stool cultures showed no pathogens and urine cultures were negative. A barium enema demonstrated several diverticula in the right colon. The roentgenogram of the chest, the intravenous pyelogram and the oral cholecystogram were within normal limits. Following discharge from the hospital on February 7, the patient continued to be afebrile; he had an excellent appetite, regained 20 pounds, and returned to work.

On September 11, approximately eight months later, he was enroute to Maine for another hunting trip; however, he returned because of a sudden onset of chills, fever and profuse diaphoresis. During the two preceding days he had noted minimal fatigue and anorexia. The shaking chills continued, lasting up to forty-five minutes; they were accompanied by a temperature of 104°F., and were followed by profuse diaphoresis. Despite this degree of fever, the patient felt remarkably well between chills. Neurological symptoms other than confusion with high fever were absent. He was nauseous and vomited only once. He thought his urine was darker than usual, but he denied jaundice. Ten days prior to admission he complained of a pain in his right shoulder which was localized to a small area posteriorly. One week before admission he was treated with 250 mg. of tetracycline-glucosamine which was administered orally every six hours for seventy-two hours. He was then referred and admitted to the Clinical Center on October 2.

A review of the patient's past history disclosed that in 1954 he had had a sudden onset of lower abdominal cramps, and at laparotomy was found to have a gangrenous diverticulum of the right colon, which was removed along with a normal appendix. Fusiform bacteria and other organisms were seen in stained

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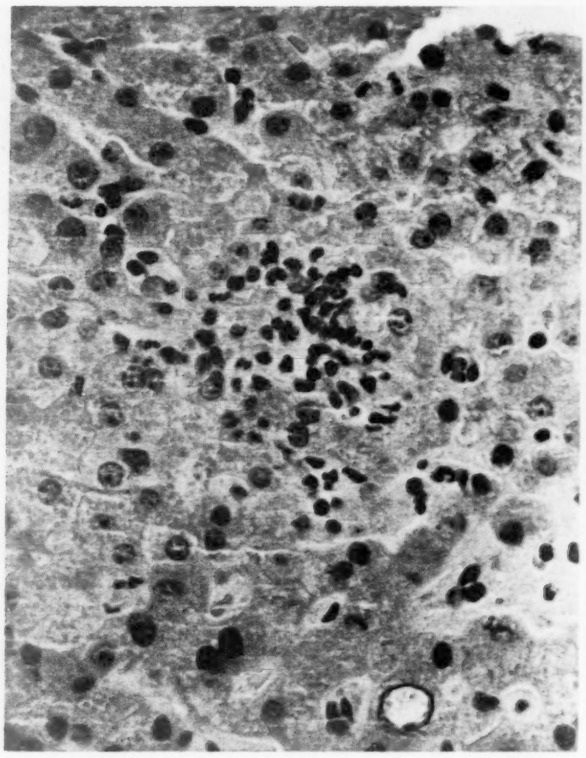


FIG. 1. Liver section. Original magnification × 440.

sections in the lumen and possibly in the wall of the necrotic diverticulum.

Physical examination revealed a febrile, chronically ill, alert man. Petechiae and spider angiomas were absent. There was minimal gingivitis and tooth No. 32 was carious. The breath was not fetid and the tonsils appeared normal. Cardiopulmonary auscultation was normal except for a few persistent dry rales over the left lower lung field posteriorly. These had been present for many years. There was no hepatosplenomegaly or abdominal tenderness. The bowel sounds were normal and the right lower quadrant scar was well healed.

Leukocyte counts varied between 13,000 and 20,000/cu. mm. with 78 per cent to 88 per cent neutrophils. The hemoglobin was 11.6 on admission but fell to 9.5 gm./100 ml. Erythrocyte sedimentation rate (Westergren method) was elevated to between 98 and 120 mm./hour. A sternal bone marrow aspiration showed granulocytic hyperplasia. The two-hour urine urobilinogen was 2.1 Ehrlich units/100 ml. initially, but was normal subsequently. The alkaline phosphatase was 4.8 Bessey-Lowry units, the total bilirubin 1.3 mg./100 ml., and the bromsulphalein 32 per cent retention in forty-five minutes. Serum glutamic oxalacetic transaminase determinations remained normal. The blood urea nitrogen, fasting sugar, cholesterol, electrolytes and amylase, and the results of urinalyses were normal. A skin test with 0.005 mg. of purified protein derivative (second strength P.P.D.) was positive. Skin tests with blastomycin, coccidioidin, histoplasmin and 0.00002 mg. purified protein derivative (first strength P.P.D.) were negative. Stool specimens were consistently negative for blood, ova, parasites and undigested meat fibers. Salmonella, brucella and Pasteurella tularensis agglutination titers were not elevated. Multiple cultures for mycobacteria and fungi were sterile.

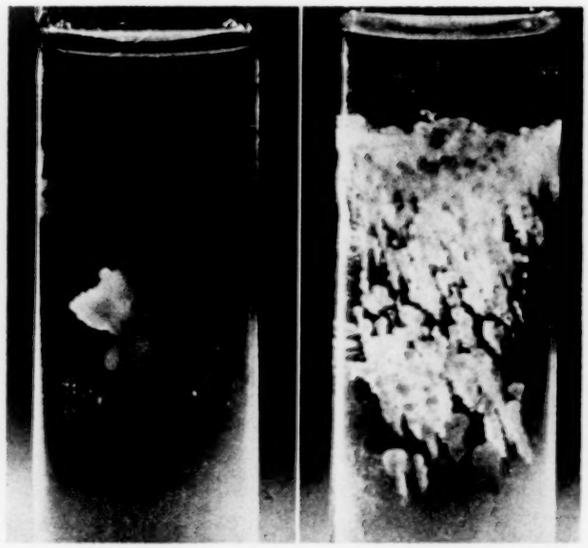


FIG. 2. Fusobacterium colonies.

Repeated attempts failed to visualize the gallbladder. A few diverticula of the right colon were demonstrated by barium enema. Films of the chest, abdomen, right shoulder, intravenous pyelogram and upper gastrointestinal series were normal. An electrocardiogram was normal.

Sections of the percutaneous liver biopsy obtained prior to treatment were examined microscopically. (Fig. 1.) Small collections of neutrophils and leukocytes were present in some sinusoids and in some periportal areas. One or two necrotic liver cells were

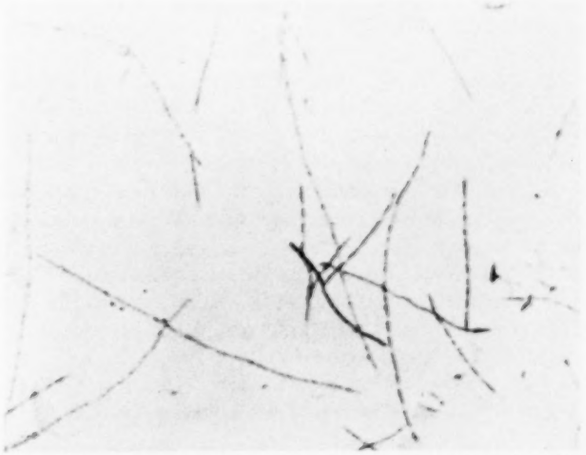


FIG. 3. Fusobacterium. Original magnification × 2040.

present within these foci. No organisms were seen in sections stained by the method of Brown and Brenn [*9*]. Findings were interpreted as those of focal necrosis with acute inflammation. With the exception of one day, during the first week of hospitalization, temperature of 102°F. or greater was present daily. On the seventh hospital day, following the report of positive blood cultures (see section on "Bacteriology"), he was given tetracycline intravenously by a slow infusion, 1 gm. every twelve hours, for a total of 3 gm. Thereafter, therapy was continued orally for fourteen days in a dose of 0.5 gm. every six hours. From the fourth day of therapy with tetracycline until discharge, he remained afebrile, and his appetite returned. A reticulocytosis occurred and the hemoglobin rose. Values for serum albumin increased from 1.7 to 2.6 gm./100 ml. Abnormal liver function tests returned to normal. At six-months' follow-up examination he remained well.

Bacteriology: Four (of six) blood cultures (October 3, 4 and 6) and a bone marrow culture (October 7) were positive for fusobacterium. Growth occurred, after forty-eight hours in thioglycollate and trypticase soy media with 0.1 per cent agar, as 2 to 4 mm. mulberry-like, whitish, butyrous, and easily emulsified colonies. (Fig. 2.) On anaerobic subculture to rabbit blood agar plates, growth appeared in two days as small, convex, ivory-colored, tenacious and strongly alpha hemolytic colonies. By stain, they were gram-negative, predominately filamentous, non-branching, rod-shaped organisms with pointed ends and reddish staining granules. The pointed ends were best seen with a two-minute crystal violet stain. (Fig. 3.) The organisms were non-motile. Biochemically, they fermented lactose, dextrose, sucrose and mannite without gas; produced H_2S; were indole positive; were methyl red and Voges-Proskauer negative; did not liquefy serum or gelatin and produced no gas bubbles from peptone media. The odor was fetid.

A rapid antibiotic disc sensitivity test was performed as follows: a heavy inoculum of fusobacteria was placed on trypticase soy agar enriched with 20 per cent human serum and incubated anaerobically for forty-eight hours. Growth of bacteria was inhibited in zones surrounding discs of penicillin (2 units), tetracycline (5 μg.), chloramphenicol (5 μg.), neomycin (5 μg.), polymyxin B (50 μg.), erythromycin (15 μg.). The organism appeared resistant, however, to streptomycin (10 μg.), kanamycin (30 μg.), vancomycin (30 μg.) and bacitracin (10 μg.). Tube dilution sensitivity tests, performed by the method of Omata [*10*] and read at four, seven and fourteen days, revealed inhibition by penicillin in concentrations of 0.78 units/ml. and tetracycline in concentrations of 0.39 μg./ml.

Pathogenicity was not noted on subcutaneous and lower lip injections into rabbits. One to two days after intracerebral inoculation two of three mice died and the brains were culturally positive for fusobacteria. Intraperitoneal and intramuscular injections into mice produced subcutaneous abscesses in a few. The organism isolated from our patient was identified as F. polymorphum by Dr. Omata [*11*].

Three serums collected during hospitalization were anticomplementary in complement fixation tests by the method of Bøe. No precipitin lines were observed by the Ouchterlony [*12*] diffusion-in-gel method with serums from this patient. Throat and fecal cultures showed normal flora. Urine, cerebrospinal fluid and liver biopsy cultures were sterile.

COMMENTS

Bacteroides, dialister, sphaerophorus and streptobacillus are included with fusobacterium in the family bacteroidaceae. Compared with the fusobacterium, bacteroides has rounded ends, dialister a smaller diameter, and sphaerophorus and streptobacillus are said to be more pleomorphic. The streptobacillus are, in addition, facultative anaerobes [*13*].

Hoffman revised the species classification of fusobacteria in Bergey's Manual as follows:

long rods, 8 to 16 μ.
  acid from maltose, F. fusiforme
  no acid from maltose, F. polymorphum
short rods, not over 4 μ.
  motile, F. praecutum
  non-motile, milk unchanged:
    stubby-spindle-shaped, F. nucleatum
    slender, pointed ends, F. vescum
    milk acidified, F. biacutum

Partly because of the difficulties in isolation and cultivation and partly because of the pronounced morphologic variability of the fusiform bacteria, the problem of classification is still in an unsatisfactory state. At present, there is no satisfactory serologic classification for fusobacteria. Excellent reviews by Bøe [*4*], Hoffman [*2*] and Prevot [*14*] may be consulted for details.

It was in the infancy of bacteriology that the fusiform bacteria were first found. It was primarily the differential diagnosis of diphtheria that attracted the great interest of investigators in this organism. Lewocwicz [*15*] in 1903 was probably the first to report the isolation of a typical fusobacterium, since Veillon and Zuber's [*16*] prior claim is in doubt in view of present day knowledge of cultures. Lewocwicz [*17*] in 1906 failed in an attempt to infect with a pure culture the mucous membranes of the mouth of a small child. E. C. Smith [*18*] in 1933 injected pure cultures into volunteer subjects and was able to

demonstrate a definite rise in temperature, which he attributed to a bacterial toxin. However, all attempts to find toxins in fusobacteria have been unsuccessful [*14*]. Bøe [*4*] in 1941 injected subcutaneously into the lower part of his arm a strain of fusobacteria isolated from a brain abscess. After about thirty hours, marked edema, redness and lymphadenopathy developed. In the course of five days a fluctuant abscess appeared on the lower part of the arm, with associated axillary adenopathy. "Stinking sero-fibrinous pus" yielding a pure culture of fusobacteria was aspirated from the abscess, showing for the first time that for man fusobacteria can be pathogenic alone as well as in association with Vincent's spirochetes or other microbes.

Omata [*10*] has studied the *in vitro* sensitivity of seven strains of fusobacteria by the tube dilution method and found penicillin to be the most effective antibiotic, inhibiting growth of these strains at 0.1 unit/ml. or less. Oxytetracycline inhibited growth at levels of from <0.5 to 2.5 μg./ml. and chlortetracycline and chloramphenicol from 2.5 to 25 μg./ml. Fusobacteria were resistant to both streptomycin and dihydrostreptomycin. Berger [*19*] confirmed these studies and also found tetracycline as effective *in vivo* as oxytetracycline. Erythromycin, neomycin, bacitracin and polymyxin B were ineffective. Foley [*20*] tested the sensitivity of B. funduliformis and B. fragilis, which are closely related to fusobacteria, to penicillin and streptomycin, and found them quite ineffective. It would appear, therefore, that if the anaerobic gram-negative, rod-shaped organism is not immediately identifiable and has not been subjected to sensitivity studies, tetracycline or oxytetracycline would be the drugs of choice in treatment of a patient.

We have found reports of fifty-three cases of fusobacterium infection in which septicemia was culturally proved or in which the presence of distant metastases was indirect evidence of blood stream invasion. Cases of otitis with meningitis or lung abscess following oral lesions or pharyngitis were considered, for the purposes of this paper, instances of direct extension of the infection, and were excluded.

Thirty-three cases represented infections with two or more organisms. Eighteen of thirty-three patients had gram-positive cocci on stained smear. When cultures were made, streptococci were found in nine, pneumococci in three, staphylococci in two and an anaerobic corynebacterium in one. In ten cases other gram-negative rod-shaped organisms were noted in conjunction with fusobacteria. Miliary tuberculosis complicated two cases, malaria one and actinomycosis one. In early studies, particularly those of Tunnicliff [*21*], the fusobacteria and Treponema vincenti were considered to be either symbiotic or the same organism in different phases, and in nine reports these two organisms were associated.

The usual clinical picture was that of a pyogenic infection, the dominating symptoms being determined by the portal of entry. In the fifty-three case reports, the original portal of entry was thought to be the gastrointestinal tract in twenty-three, the appendix accounting for sixteen of these; the lung in eighteen; the oropharynx in five; ear or sinus in three; endometrium in two; the site of a rat bite and unknown in one. Of the two reported cases of endometritis with apparent septicemia, both represented infections with mixed flora. The urinary tract as a primary site of infection has not been reported.

Fusobacterial infection should be suspected in any patient with fetid otitis or sinusitis. There are numerous case reports of fusobacterial otitis media or sinusitis complicated by meningitis, brain abscess and lung abscess. These, however, probably represent direct extension or aspiration and were not included as septicemia in the absence of positive blood cultures. Burnes et al. [*22*] in 1958 reported three cases of their own of eye involvement and nineteen additional cases from the literature.

Twenty of the fifty-three cases confirmed by either a positive blood culture or a metastatic abscess, thought to contain only fusobacteria by culture, are shown in Table 1. Six cases were proved by one or more blood cultures. It is of interest that in our patient (Case 20) blood cultures were positive as late as the twenty-sixth day of illness. When sufficient data were given in other cases of culturally proved septicemia, positive blood cultures were obtained on the forty-sixth (Case 13) and ninth (Case 16) hospital days.

Fifteen of the twenty patients were males, and the youngest were females. Their ages were as follows: Two were four and five; one-half were between forty and sixty; the oldest was sixty-six. Race was mentioned in only a few instances. It is probable from the clinical data that all were

TABLE I

CASES OF FUSOBACTERIUM SEPTICEMIA

Case No.	Author, Date, Reference	Age (yr.) and Sex	Clinical Data	Outcome	Duration of Illness	Portal of Entry	Pathologic Data	Bacteriology		
								Smear	Culture	Blood Culture
1	Berestnew 1898 [23]	5, F	Had fetid sputum, lung abscess, empyema and septicemia	Died	5 mo.	Lung	Empyema Lung abscesses, bilateral Brain abscess, occipital	+* + +	 +	
2	Silberschmidt 1901 [24]	58, M	After being treated for "lung disease," became transiently unconscious; the following day he noted foul sputum and incapacitating pain in the left thigh; subsequent incision of a thigh abscess released a large amount of red-brown foul pus	Died	?2 yr.	Lung	Left thigh and knee joint abscess Bronchiectasis Brain abscess, occipital	+* +		
3	Kasper and Kern 1910 [25]	50, F	Had acute peritonitis	Died	7 days	Appendix	Appendiceal abscess Liver abscess Lung abscess, middle lobe of right lung Pylephlebitis and peritonitis Cholelithiasis and hydrops Splenomegaly with infarcts	 + +*	 + 	
4	Frühwald 1913 [26]	4, F	Had three episodes of purulent meningitis, each followed by apparent recovery; an aspirated needle that formed a fistulous tract from the posterior pharyngeal wall to the cervical spine was incriminated; terminally, signs of a brain abscess developed	Died	3 mo.	Pharynx	Purulent bronchitis Brain abscesses, temporal lobe and hypophysis Meningitis Fistula, pharynx to spinal cord		+ 	
5	Larson and Barron 1913 [5]	37, M	Had a sudden chill, septic temperature and night sweats, occasional malaise; severe pyorrhea alveolaris, foul breath, extensive ulceration and necrosis of the upper jaw were noted; clinically, he showed only minimal discomfort, but after seven weeks became gradually comatose	Died	7 wk.	Mouth	Pyorrhea alveolaris Buccal gangrene Maxillary osteomyelitis	+		+
6	Dick 1914 [27]	40, M	Had severe left-sided headaches and speech difficulty following drainage of a fetid temporosphenoidal abscess; chronic bronchitis preceded the illness	Died	3+ mo.	Lung ?intestine	"Chronic follicular enterocolitis" Brain abscess, cerebral	 +	 +	
7	Maresh 1916 [28]	17, M	Had a three-year history of abdominal pains and vomiting, and a six-week history of chills	Died	?6 wk. ?3 yr.	Appendix	Appendix obliterated and surrounded by adhesions Pylephlebitis Liver abscesses	 +	 +	
8	Maresh 1916 [28]	51, F	Had "temporary irritation of the cecum," and four months later a gangrenous appendix was removed; the following month fever, chills, anorexia, vomiting jaundice, and an enlarged tender liver developed	Died	6 mo.	Appendix	Retrocecal abscess, appendectomy site Pylephlebitis Liver abscesses	 +	 +	

* Mixed flora.

TABLE 1 (*Continued*)

CASES OF FUSOBACTERIUM SEPTICEMIA

Case No.	Author, Date, Reference	Age (yr.) and Sex	Clinical Data	Outcome	Duration of Illness	Portal of Entry	Pathologic Data	Bacteriology		
								Smear	Culture	Blood Culture
9	Maresh 1916 [28]	50, M	Had an illness characterized by increasing periumbilical pain, vomiting, anorexia, a 12 kg. weight loss, chills, and fever varying between 38° and 39°C.	Died	3 mo.	Appendix	Colon abscess Appendix adherent to cecum Peritonitis and adhesions Pylephlebitis Liver abscesses	+	+	
10	Ghon and Roman 1916 [29]	39, M	Had gradually increasing signs of "lung inflammation"; because of subcostal pain and dysuria a laparotomy was performed and multiple liver abscesses were drained	Died	3 mo.	Rectum	Rectal abscess with perforation and periproctitis Pylephlebitis and peritonitis Gallbladder wall abscess Splenomegaly Liver abscesses	+	+	
11	Ghon and Roman 1916 [29]	53, M	Had jaundice diagnosed as "cholecystitis and sepsis"	Died	5 wk.	?intestine	Carcinomatous ulcerating rectal polyp Ileal and ileocecal valve scars Cholelithiasis and obstruction of bile duct Splenomegaly Liver abscesses	+	+	
12	Coronini and Priesel 1920 [30]	66, M	With a long history of chronic bronchitis and emphysema had a recurrence of fetid sputum shortly before death	Died	3 mo.	Lung	Lung abscess, middle lobe of right lung Gangrenous pneumonia, middle and lower lobes of right lung Bronchitis Cerebral abscess	+*	+	
13	Smith 1927 [6]	42, M	Noted severe chest pain, followed in eight weeks by increasing cough and sputum production, fever, profuse night sweats and weight loss; five months later there was consolidation of the upper left lobe, clubbing of fingers, and cyanosis; his temperature varied between 101° and 103°F.	Died	1 yr.	Lung	Carcinoma of the lung Lung abscess			+
14	Brocard and Daum 1941 [31]	50, F	Had fever and pleurisy with a large pulmonary abscess; fever abated after needle aspiration of the abscess; two months later localizing neurological signs and recurrent fever indicated a brain abscess which subsequently was drained surgically on three occasions	Died	1 yr.	Lung	Lung abscess, lower lobe of right lung Brain abscess, temporal	+	+	
15	Williams 1941 [7]	28, M	Was acutely ill seven weeks, became afebrile and mentally clear following a tonsillectomy; his course was complicated by gonorrheal urethritis and serologic evidence of brucellosis; following hyperthermia, treatment of the urethritis, he had nausea, epigastric distress, chills, temperature elevations to 104°F., transient jaundice, a pleural friction rub, and a rash over the legs and trunk	Lived	?6 mo.	Tonsils				+

TABLE 1 (*Continued*)
CASES OF FUSOBACTERIUM SEPTICEMIA

Case No.	Author, Date, Reference	Age (yr.) and Sex	Clinical Data	Outcome	Duration of Illness	Portal of Entry	Pathologic Data	Bacteriology		
								Smear	Culture	Blood Culture
16	Williams 1941 [24]	24, M	One month following a rat bite of his finger, complained of acute pain and swelling in the left hip, preceded for four days by fever, chilliness, anorexia, nausea and myalgia; a transient migratory and inflammatory arthritis followed; temperature between 101° and 103°F. lasted two weeks, then gradually subsided	Lived	?2 mo.	Rat bite				+
17	Brocard, Choffel and Bouvier 1954 [8]	46, M	Had a twelve-year history of intermittent fetid and bloody sputum, was hospitalized because of pleuritic pain, purulent sputum, pneumonitis, hepatomegaly, and metastatic subcutaneous abscesses over the left shoulder and right forearm; the abscesses contained only fusobacteria; fever abated with penicillin therapy, but the shoulder abscess remained infected and was drained; oxytetracycline and chlortetracycline treatment was followed by clearing of the chest film and return of the white cell count to normal	Lived	5 mo.	Lung	Pneumonitis, apical segment, lower lobe of left lung Subcutaneous abscesses right forearm left shoulder	 + +	 + +	
18	Caroli, Paraf, Eteve and Prevot 1956 [8]	58, M	Past history of alcoholism, had the sudden onset of chills, temperature to 40°C., right lower quadrant pain, and jaundice; uremic cholangiolitis was diagnosed and penicillin therapy prescribed; three days later because of rapidly increasing jaundice and hepatomegaly without tenderness, chloramphenicol was substituted; he died following drainage of multiple liver abscesses	Died	10 days	Cecum	Cecal ulcers, 1 cm., hemorrhagic, necrotic and "typhoid-like" Liver abscesses, multiple	 +	 +	
19	Caroli, Paraf, Eteve and Prevot 1956 [8]	?, M	Had a febrile illness characterized as "febrile anemia"	Lived	?	Buccal				+
20	Tynes and Utz	46, M	See case presentation	Lived	?1 yr.	?Intestine	Diverticulitis Focal necrosis with acute inflammation of liver			 +

* Mixed flora.

febrile. The fever was usually septic and in most instances the temperature reached 104°F. with morning remissions. Eight patients had chills, but only four were noted to have profuse sweats.

The ninth-month interval between illnesses in the patient described herein is intriguing. In Cases 4 and 14 the intervals of apparent "recovery" were similar but shorter. The indolence of fusobacterial infections is illustrated by Case 9 in which the originating appendiceal

infection and pylephlebitis appeared histologically old and inactive, whereas the metastatic lesions progressed. The sense of well-being in our patient during the illness was striking. Case 5 also suggested this paradox.

It seems to us that our patient's origin of infection was gastrointestinal because of his history of gangrenous diverticulitis and the demonstration of the fusiform bacteria in sections of the bowel. In the eight other cases in which the lower gastrointestinal tract was the probable origin of infection, all patients had abscesses of the liver and five were icteric. Tenderness of the liver was present in two and absent in two. The only comparable histologic report on fusobacterium involvement of the liver is that of Caroli et al. (Case 18) in which rounded cheesy abscess cavities were surrounded by a moderate inflammatory reaction with a narrow border of migratory cells. Five patients had pylephlebitis and three had peritonitis. Cholelithiasis was a complication in two of the patients, with one of these having obstruction of the common duct. Septicemia in Case 10 probably had its origin in a shallow rectal ulcer.

It seems less likely to us that the portal of entry in our patient was his carious tooth. That oral cavity lesions may cause septicemia is illustrated by Case 5. Fusobacteria are normally present in the upper respiratory tract, but do not inhabit the lower tract except in disease. A pulmonary origin was probable in seven cases, and nine patients had pulmonary involvement at some time. All but one of the patients with a pulmonary origin had a brain abscess. There was fetid sputum in five and hemoptysis in one of these patients. Four had abscesses in the lung and three had bronchiectasis or pulmonary gangrene.

One can only speculate on the association of the owl skinned by our patient and the disease which developed ten days later. In Case 16 a rat bite was considered to be the portal of entry. Fusobacteria are commonly found in the alimentary tract of warm-blooded animals.

Laboratory data in the cases reported were generally meager. The leukocyte count of seven patients varied from 2,400 cu. mm. (Case 5) to 60,000 cu. mm. (Case 13). Treatment consisted of surgical drainage and the administration of heavy metals or antibiotics. In Cases 13, 15 and 16 arsphenanine was used. In Cases 17, 18, 20 and probably 19 antibiotic therapy was used; all but one of these (Case 18) survived.

SUMMARY

Fusobacterium septicemia, corroborated by four positive blood cultures and a positive bone marrow culture, occurred in a forty-six year old man. The organism was identified as F. polymorphum. The illness was characterized by high fever, shaking chills and profuse diaphoresis. Leukocytosis, anemia, elevated erythrocyte sedimentation rate and abnormal liver function tests were present. Biopsy of the liver showed focal necrosis and acute inflammation. Tetracycline therapy, administered intravenously for thirty-six hours and orally for fourteen days thereafter, was associated with clinical recovery, negative blood cultures and return to normal of laboratory findings.

Fifty-three cases of fusobacterium septicemia, of which twenty represented infection by that organism alone, were collected from the literature. Positive blood cultures or presence of distant metastases were considered evidence of septicemia. Analysis of these cases disclosed striking similarities. The most outstanding of these are (1) a gastrointestinal or pulmonary site of origin; (2) metastases to the liver or brain; (3) poor prognosis without antibiotic therapy.

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Occurrence of Retinal Pigmentation, Ophthalmoplegia, Ataxia, Deafness and Heart Block*

Report of a Case, with Findings at Autopsy

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In 1946 Refsum [*1*] described five patients with night blindness, impaired vision, retinal pigmentation, deafness, ataxia, and a form of polyneuritis in which the spinal fluid protein content was increased. Subsequently, other similar cases were reported [*2–9*]. Pathologic studies suggested that Refsum's syndrome is a form of interstitial polyneuritis [*3,10,11*].

Recently, a thirteen year old boy with many of the previously noted features of this syndrome offered us unusual opportunities for study of the disorder. First, scrutiny of numerous photographs provided by the family yielded a means of determining the time of onset and manner of progression of certain symptoms. Secondly, this boy, previously in good health, was observed closely during a period of two weeks in which impaired conduction of cardiac impulses resulted in his death. It was believed that this cardiac difficulty was an intrinsic part of the illness. Finally, careful studies performed postmortem revealed few abnormalities despite the striking clinical manifestations. Certain peculiarities in this case as related to Refsum's syndrome and to other syndromes will be considered briefly.

CASE REPORT

J. W., a thirteen year old boy, was referred to the hospital for management of suspected myasthenia gravis. At about the age of ten years the patient was observed by his family to have difficulty in hearing and limitation of the movement of the muscles of his eyes. During the next several years weakness of the muscles of the mouth became evident. These symptoms did not vary greatly in severity throughout the day. Dysphagia, speech difficulty, inability to hold the head up, trouble in chewing and peripheral weakness did not occur. Night blindness was not present. A physician who saw the patient at twelve years of age suspected myasthenia gravis and instituted therapy first with the administration of oral neostigmine and subsequently with pyridostigmine, without definitive results; however, the latter medication was continued to the time of admission to the hospital. In the last year the family had noted that the patient's hand movements and gait were incoordinated. The patient's strength and muscular development were not thought to be affected. His work at school was considered to be adequate and he was in the proper grade for his age.

Photographs of this patient taken at various ages (seven, eight, nine, ten, eleven, twelve and a half and thirteen years) are shown in Figure 1. At ten years of age, ptosis of the lids and a transverse smile were noted. These became progressively more evident in the pictures taken at eleven and at twelve and a half years of age. The final portrait was taken at age thirteen at the time of the first admission to the hospital.

The past history was non-contributory. The boy developed normally, although he was regarded as small for his age. Previous illnesses included measles, varicella and mumps, none of which was unduly severe. There was no history of encephalitis.

The family history disclosed only that a paternal grandmother and a maternal aunt had diabetes

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FIG. 1. The bilateral ptosis and the transverse smile are first apparent at ten years of age.

mellitus. There was no history of consanguinity. The parents and the patient's three brothers, ages six, ten and eighteen years, and one sister, age seventeen years, were in good health. Examination of all of the siblings and the parents was within normal limits.

The physical examination of the boy showed a somewhat poorly developed adolescent measuring 145 cm. (57 inches) in height and weighing 29.9 kg. (64 pounds). The pulse, blood pressure and respiratory rate were within normal limits. Examination of the heart, lungs and abdomen was non-contributory. The testes were small and there was no secondary sexual development. There was a pronounced ptosis of both eye lids and the range of movement of the eyes in all directions was restricted to less than 10° from the usual forward gaze. (Fig. 2.) There was no nystagmus. The pupils were equal in size and reacted promptly to light and accommodation. Ophthalmoscopic examination disclosed normal optic discs and normal appearing retinal vessels. Beginning several disc diameters away from the nerve head and extending peripherally as far as could be visualized, the retinas were studded with minute black flecks of pigment which were no greater in diameter than the width of a retinal artery and had no corpuscular configuration. There was no myopia and no evidence of cataract. The transverse configuration of the lips disclosed the weakness in the orbicularis oris and examination showed the orbicularis oculi to be weak also. Moderate reduction in hearing was present bilaterally. Anosmia was not detected and no other cranial nerve impairment was evident. The muscles of the trunk and extremities were poorly developed. All tendon reflexes and superficial reflexes were intact. No pathologic reflexes were elicited. Sensory examination was completely within normal limits. There was a slight bilateral intention tremor on heel-to-knee and finger-to-nose maneuvers. The gait seemed normal.

Routine laboratory studies of the blood and urine were non-contributory. Roentgenograms of the chest and skull revealed no abnormalities. An agglutination test for toxoplasmosis and complement fixation tests for western and eastern equine encephalitis and for syphilis had negative results. Visual fields with a Bjerrum screen were normal. Visual acuity was 20/20 in the left eye and 20/30 in the right eye. There was no color blindness (American Optical Company Color Blind Chart). Audiometric studies showed bilateral partial nerve deafness. Examination of the spinal fluid revealed a protein of 115 mg. per 100 ml. without other changes.

Tests designed to prove or disprove the presence of myasthenia gravis in this patient gave only negative results. The withdrawal of pyridostigmine medication for twenty-four hours was without effect. Parenteral administration of neostigmine after this period did not produce an increase in strength or any change in the severity of the ophthalmoplegia. Administration of quinine (0.6 gm. orally) and subsequently of d-tubocurarine (2.2 mg. intravenously over a one minute period) caused no weakness.

The patient was discharged on the third hospital

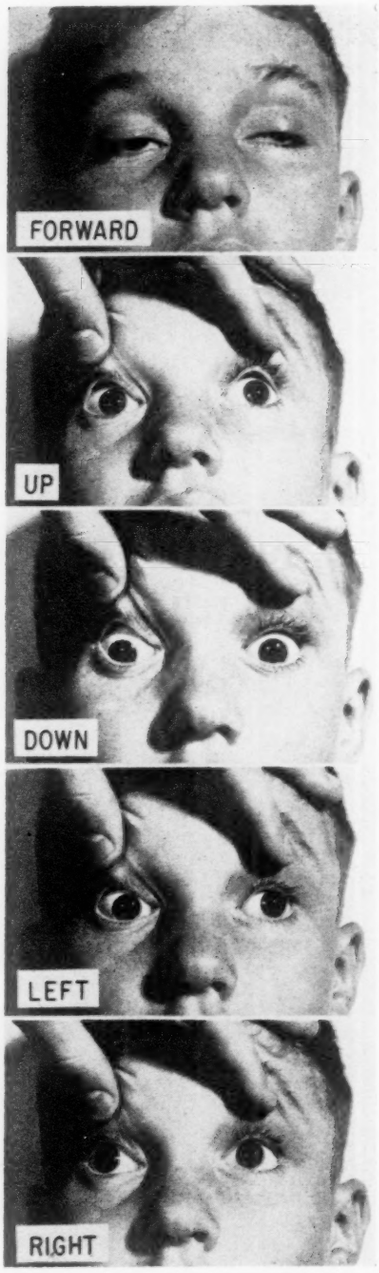


FIG. 2. Note the almost complete external ophthalmoplegia at the time of the patient's first admission.

day and was instructed to discontinue pyridostigmine therapy. There was no change in the status until two months later when the boy was readmitted to the hospital because of nausea, vomiting and frequent formed bowel movements. These complaints were of four days' duration and had appeared without antecedent fever or malaise. No other member of the family gave a history of recent illness. At this time the child appeared listless. The temperature was 97.4°F., pulse 28, and respirations 12 per minute. In contrast to the findings of the previous admission, the heart now seemed slightly enlarged and there was a prominent systolic murmur along the left sternal border. The first heart sound at the apex varied in intensity. The lungs were clear. There were no signs of heart failure. The neurologic examination was unchanged.

Laboratory studies now showed a packed red cell volume of 45 per cent, a total white blood cell count of 7,600 per cu. mm. and a differential count of 52 lymphocytes and 48 neutrophils. Examination of the urine had negative results. Cultures of the urine were sterile and stool cultures grew no pathogenic bacteria. Results of a Schick test were negative. A single serum specimen contained no agglutinins against the Brucella, typhus, typhoid, paratyphoid or tularensis organisms. The fasting blood sugar, blood urea nitrogen, carbon dioxide combining power, serum chloride and bromsulphalein retention were within normal limits. The antistreptolysin O titer was 1:166. Subsequent white blood cell and differential counts were normal on three occasions. First and second strength tuberculin skin tests (purified protein derivative) had negative results.

Serial electrocardiograms disclosed A-V conduction defects ranging in severity from first degree to complete heart block. However, on one occasion complete right bundle branch block with normal A-V conduction was present.

For the first three days the patient was apathetic. He was treated with oral ephedrine tablets and later with isoproterenol (Isuprel®) with apparent decrease in the degree of heart block. Because of the possibility that a rheumatic, viral or idiopathic myocarditis might be present, he was then treated with the oral administration of prednisone in a dose of 5 to 10 mg. daily. He seemed to improve but subsequently had a recurrence of his conduction defects and died on the fourteenth day. There was no fever at any time during hospitalization. No symptoms of systemic illness apart from the cardiac disorder were present. The abdominal pain and frequent bowel movements did not continue after he was admitted to the hospital.

The postmortem examination* disclosed few abnormalities in this boy. The ventricles of the heart were dilated but not thickened. The heart weighed 200 gm. The pericardium, myocardium, endocardium, valves and coronary vessels were normal. The lungs showed only minimal congestive changes. The other viscera, including thyroid, adrenal, testes, pancreas and bowel, were normal. There was atrophy of the thymus gland. Multiple sections of the heart and sections of other organs appeared normal on microscopic examination.

Grossly, the brain, spinal cord and peripheral nerves were not unusual. No thickening of peripheral nerves was observed. Histologically, sections of the brain and spinal cord stained for myelin, fat and Nissl substance showed no abnormalities. The myelin

* Performed by David K. Miller, M.D.

sheaths of the nerves in the superior rectus eye muscle stained with a fine irregularity, but no material was obtained for fat stains on this tissue specimen. Other peripheral nerves showed no changes. There seemed to be patchy atrophy of extrinsic eye muscles and some of the remaining eye muscle fibers stained poorly with phosphotungstic acid-hematoxylin stain. Sections of other skeletal muscles were normal. There was no discernible histologic difference between sections of the patient's eyes and those of a control subject without retinal pigmentation.

In summary, this thirteen year old boy seemed to be the only affected member of his family. His symptoms included drooping of the eyes and slight ataxia. On examination he was found to have almost complete external ophthalmoplegia, a nerve type of deafness, retinal pigmentation, facial weakness and minimal ataxia. An elevated spinal fluid protein (115 mg. per 100 ml.) was the only unusual laboratory finding. Several months after his initial examination, and at least three years after the onset of any symptoms, varying degrees of heart block developed and he died. Clinically as well as pathologically there was no explanation for the heart disorder. Autopsy studies showed only patchy atrophy of extraocular muscles and no retinal changes. In particular, no thickening of nerves was observed grossly, and on histologic section no concentric proliferative changes in the sheaths of peripheral nerves were demonstrated.

COMMENTS

From perusal of twenty-two previously reported cases of Refsum's syndrome [*1–9*], it is evident that certain features are relatively constant whereas others are variable. This disorder is thought to be inherited as a recessive trait. There is no sex predominance. A history of consanguinity usually was obtained when more than one sibling in a family was affected. Often the first symptoms appeared in the first or second decade. Disturbance of vision, particularly night blindness, commonly was the earliest manifestation. Less often, impairment of gait due either to weakness or ataxia ushered in the syndrome. Occasionally progressive reduction in hearing was the initial complaint.

On examination, nerve-type deafness and retinal pigmentation were frequent findings. The fundi showed pigmentation which was regarded as atypical for the usual retinitis pigmentosa in that no corpuscular configuration of the pigment was detected. Not uncommonly, the retinal vessels appeared narrowed. On testing, reduction in the peripheral visual fields often was present and was associated at times with reduced visual acuity or even blindness. Posterior cataracts and myopia were observed occasionally. Sometimes the optic disc was pale. Sluggishly reacting pupils occurred often. Other findings relating to the neuromuscular system consisted of muscular atrophy, reduced or absent tendon reflexes, and varying degrees of incoordination. Frequently, reduction in strength was greater in the peripheral portions of the limbs; it was associated with varying degrees of sensory impairment and seemed to be similar to the findings of peripheral neuritis as it appears with various systemic diseases. Inconstant features were ichthyosis, anosmia, and developmental anomalies of the skeletal system.

With few exceptions, examination of the spinal fluid revealed a striking increase in protein without other abnormalities. In approximately one-third of the patients there were minor electrocardiographic disturbances which usually consisted of impaired conduction within the ventricles.

The course of the disorder is usually progressive but may be remittent. Sudden or unexpected death occurred in at least six of the twenty-two patients.

The pathologic findings in Refsum's syndrome are few and relate primarily to the peripheral nerves which often were found to be thickened. On section, the nerves showed concentric sheath proliferation, a finding also present in hypertrophic interstitial neuritis of Déjerine and Sottas [*10–12*]. Reference to the heart is rare. In one case recorded by Reese and Bareta [*3*] there was moderate vacuolation and basophilic degeneration of cardiac muscle fibers. In one case reported by Gordon and Hudson [*9*] the microscopic examination of the heart is described as follows: "In large areas, heart muscle fibers seem to have lost much of their identity in a kind of syncytium."

The case described herein possessed some of the features of Refsum's syndrome and was unusual in certain other respects. Certainly, the retinal pigmentation, nerve-type deafness, ataxia, elevated spinal fluid protein, electrocardiographic changes and mode of death seem consistent with this syndrome. The lack of the disease in other members of the family could be ascribed to the fact that it is transmitted as a recessive trait. Unusual for Refsum's syndrome were the absence of a history of night blindness, the lack of pupillary abnormalities, the lack of constriction of visual fields, the absence of ichthyosis, the failure to detect convincing evidence of periph-

eral neuritis as judged by intact tendon reflexes and lack of sensory deficit, and finally by the inability to demonstrate perineural proliferative changes on postmortem examination. The facial muscle weakness and the external ophthalmoplegia also would be unusual in this syndrome, although these two findings were present in a case of this syndrome described by Oleson [*6*].

In certain respects our patient resembled those in whom ophthalmoplegia and retinal pigmentation coexisted. Such cases, as listed by Bernard and Scholz [*13*], Walsh [*14*], Chamlin and Billet [*15*], De Ruyter [*16*], Alfano and Berger [*17*], all share in common these two features but differ one from another in many aspects. Thus, some of these patients gave a history of night blindness, had retinal pigmentation atypical for retinitis pigmentosa and showed constricted visual fields and narrowed retinal vessels. However, as in our case, other patients with similar retinal pigment gave no history of night blindness and had normal visual acuity and visual fields. The pigmentation of the retina and the ophthalmoplegia in some of these cases were accompanied by other symptoms such as nerve-type deafness, paralysis of the ninth cranial nerve, clonus, and weakness of the facial muscles [*14*]. In two instances the spinal fluid was said to be normal [*13,17*]; in other cases, the studies of spinal fluid and certain other clinical features were not mentioned and the omission makes it difficult to compare the findings with those described in the present case report.

Typical and atypical retinitis pigmentosa are known to occur in a number of syndromes reported by Kjerrumgaard [*18*] but only those mentioned previously appear to have close resemblance to the case in point. Further, in certain instances of hereditary ataxia, particularly of Friedreich's ataxia, features such as retinal pigmentation, or rarely the finding of an elevated cerebrospinal fluid protein may appear [*19*]. Sandifer [*20*] described a twenty-nine year old man in whom ophthalmoplegia was accompanied by bradycardia and electrocardiographic evidence of conduction defect.

Cobb [*21*] attempted to resolve some of the complexities of the multiplicity of neural atrophies. He indicated that many of these were comprised of varying combinations of a total of eighteen different lesions. It seems probable that a similar situation exists in the present syndrome; in our case benign retinal pigmentation, ophthalmoplegia, nerve-type deafness, facial weakness (neural or myopathic), ataxia, abnormal cardiac conduction and an elevated cerebrospinal fluid protein content were components. It would not be unexpected that there should be related cases with differing features. It would have been desirable but it was not possible to detect specifically in our patient whether or not the ophthalmoplegia and the facial weakness were myopathic or neural in origin, whether or not the cardiac conduction defect represented some definite form of myocardial damage (not demonstrable by histologic technics) and what lesion was the source for the mild ataxia.

SUMMARY

A thirteen year old boy presented with facial weakness, ophthalmoplegia, retinal pigmentation, nerve deafness, mild ataxia and an elevated spinal fluid protein. Subsequently, there were disturbances in cardiac conduction with fatal outcome. Postmortem studies disclosed only minor changes in the extrinsic muscles of the eye and gave no clue as to the etiology of the cardiac conduction defect. No changes were demonstrated in the central nervous system or in the peripheral nerves. The length of illness and its progression suggest that in this case a familial disorder is represented which has clinical similarity to cases reported previously under the term, Refsum's disease or heredopathia atactica polyneuritiformis.

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Systemic Mast Cell Disease*

Physiologic Considerations and Report of a Patient Treated with Nitrogen Mustard

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URTICARIA pigmentosa has been recognized as a clinical entity by dermatologists since 1878 [*1*]. It occurs most frequently as a benign skin condition in childhood, usually within the first year of life, causes little difficulty, and disappears in later years. Adult forms are recognized. Although several morphologic types of skin lesions have been described, the disease most often appears as a widespread macular or papular eruption, with mast cell infiltration as a common denominator.

The mast cell is a pleomorphic, often irregularly shaped cell with pale cytoplasm packed with large metachromatic granules which may partially obscure visualization of the round or oval nucleus. Normally, this cell is found in small numbers in connective tissue and in groups around blood vessels. It is thought to arise from fibroblast-like stem cells or from undifferentiated cells within blood vessel walls [*2*]. The morphologic structure of the mast cell differs from that of the blood basophil, which is smaller and has a lobulated nucleus. Although the granules of the basophil resemble those of the tissue mast cells in staining properties, they are distributed irregularly within the cell [*3*]. Basophils arise from the bone marrow. Smyth and Gum [*4*] have called the mast cells "unicellular glandular organs." They have been implicated as the source of histamine, heparin, serotonin and hyaluronic acid, thus assuming considerable physiologic and pathologic importance.

That mast cell infiltration may be present as a widely disseminated disease, rather than localized to cutaneous structures, was demonstrated by the case report of Ellis [*5*]. In this case mast cell infiltrations were found in many organs including the bone marrow, lymph nodes and liver, the latter also showing cirrhotic changes. Sagher [*6*] reported on the bone lesions found in this disease. Several case reports of systemic mast cell disease in association with urticaria pigmentosa have since appeared. These have been recently summarized by Nickel [*7*] and Beare [*8*].

We have had the opportunity to observe and study an adult patient with mastocytosis, which forms the basis of this report.

CASE REPORT

A sixty year old white male shipping clerk and barkeeper was first seen in 1952 regarding the possibility of treatment for a hemangioma of the face. This represented a birthmark of the right lower lip which had slowly increased in size throughout life. His history revealed persistent pigmented asymptomatic skin lesions of the trunk and proximal extremities for a period of ten years. For many years he had suffered occasional short attacks of tachycardia, which he terminated by the Valsalva maneuver. He had recurrent vague pain in the right upper quadrant of the abdomen.

During routine physical examination in 1952 hepatosplenomegaly was discovered. The spleen was hard and extended below the level of the umbilicus. The liver was firm, regular, and was felt 3 cm. below the costal margin. A large hemangioma of the right region of the chin was described as well as a "discrete macular erythematous eruption of the skin of the trunk and upper extremities." Liver function tests revealed a 1 plus cephalin flocculation test but the result of serum total proteins, albumin, globulin and alkaline phosphatase tests were normal. An upper gastrointestinal series revealed a hiatal hernia. Since the hemangioma was believed to be benign, no treatment was recommended. A diagnosis of "alcoholic cirrhosis" was offered to explain the hepatosplenomegaly.

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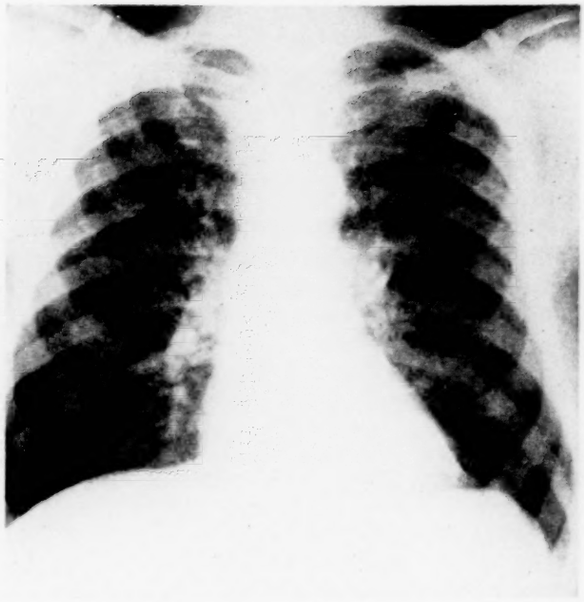


FIG. 1. Roentgenogram of the chest showing multiple small radiolucent areas of ribs resulting in a lacy appearance.

In March, 1958 he was referred to us for re-evaluation of the hemangioma which was thought to be enlarging. His general health had remained good, although some abdominal discomfort had continued and he had lost some thirty pounds during the six year period. There was no history of diarrhea. The skin eruption had remained about the same.

Physical examination revealed a plethoric, well developed and nourished white man who appeared well. A large fungating purple hemangioma some 5 cm. in diameter occupied areas of the right chin and lower lip. A firm smooth spleen extended 21 cm. and the liver extended 15 cm. below the costal margin. There was deformity of the left knee from an old injury. The skin of the trunk and proximal portions of the upper extremities revealed a patchy discrete macular erythematous dermatosis with brownish discoloration of some of the lesions, most marked over the scapular areas. After stroking the skin the pigmented and erythematous lesions became urticarial.

Laboratory data revealed the following: the hemogram revealed no abnormalities, and differential blood counts were normal with only a rare basophil, but no tissue mast cells. Results of urinalyses were normal except for occasional 1 plus protein reaction. A cephalin-cholesterol flocculation test was 2 plus and a bromsulfalein test showed a forty-five minute retention of 7 per cent (normal value: 5 per cent). The prothrombin time was sixteen to eighteen seconds with a control of fifteen seconds. The blood glucose was 80 mg. per cent; non-protein nitrogen, 36 mg. per cent; uric acid (several determinations), 7.2 to 8.5 mg. per cent; serum albumin/globulin, 4.2/1.6 gm. per cent; serum calcium, 10.6 mg. per cent; alkaline phosphatase, 7.9 King-Armstrong units; serum bilirubin, 0.6 mg. per cent; serum protein electrophoretic pattern, normal; total cholesterol, 111 mg. per cent; free cholesterol, 40 mg. per cent. The electrocardiogram revealed no abnormalities. Roentgenograms of vertebrae, ribs, long bones and skull all revealed some diffuse increase of density with multiple small radiolucent areas. (Fig. 1.)

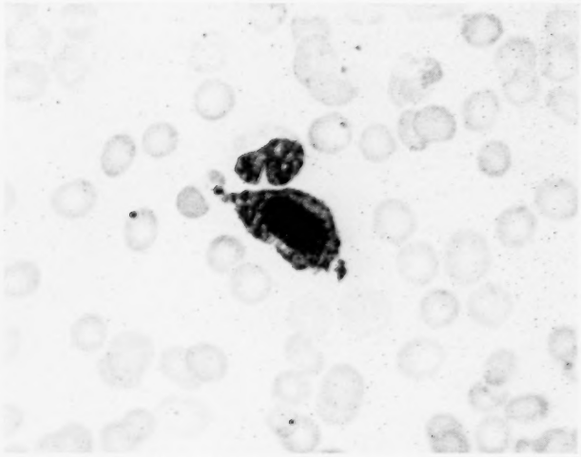


FIG. 2. Large irregular mast cell obtained from bone marrow.

Bone marrow aspiration was normal except for the presence of 2 to 4 per cent mast cells. (Fig. 2.) Splenic puncture revealed 3 per cent mast cells; the remaining cells were those normally seen in splenic aspirates.

An open liver biopsy was performed since the possibility of hemangioma of the liver was entertained. At laparotomy the liver was large, with a smooth edge. Liver sections stained with hematoxylin and eosin revealed no abnormalities, but toluidine blue stains revealed numerous infiltrations of mast cells staining metachromatically. (Fig. 3.) A biopsy specimen of the skin revealed typical mast cell infiltration in the dermis.

The patient's skin was vigorously rubbed with a coarse towel and blood was tested for heparinoid substances by the technic of Jaques [*56*]. There was no change in the clotting times or concentrations of lipemia-clearing substances following this procedure.

The resting urinary excretion of free and conjugated histamine was within normal limits as determined by the methods of Code [*57*] and Roberts and Adam [*59*].

The patient was given 100 mg. of hydrocortisone intravenously and serial clotting times were performed. Two hours later another 100 mg. of hydrocortisone was given intravenously. One and a quarter hours after the second infusion there was a transient elevation of the Lee-White clotting time from 6.9 minutes to 17.7 minutes. At the same time heparinemia was demonstrable, corresponding to 0.002 mg. heparin per ml. of plasma. On another day an

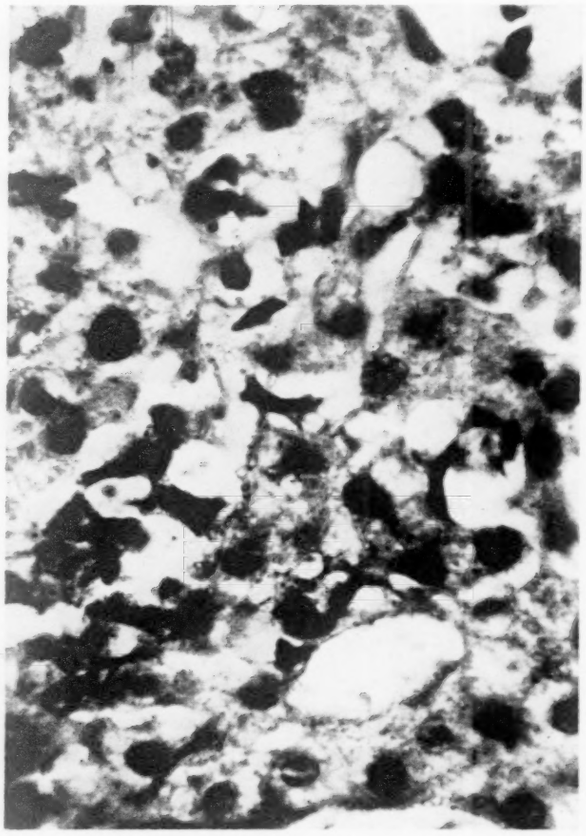


FIG. 3. A section of the liver with mast cells scattered throughout, forming a nest in left lower corner.

intravenous injection of 100 mg. of hydrocortisone increased the Lee-White clotting time from 9.2 to 13.2 minutes. He was then given prednisone orally, 75 mg. per day for ten days. There was no diminution of the size of either the spleen or liver during this therapy, which was thereafter discontinued.

The patient was then given slowly increasing doses of intravenous nitrogen mustard, for a total of 0.4 mg. per kg. administered over a three day period, receiving 0.2 mg. per kg. as a single infusion on the last day of therapy, at which time careful monitoring of clotting times revealed no release of circulating heparinoid substances. Resting urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid assayed by the method of Udenfriend et al. [*58*], was found to be normal; no increase was noticed during the nitrogen mustard treatment. No increase in plasma histamine levels was observed during mustard therapy.

Following the treatment with nitrogen mustard there was a decrease in the size of the spleen and liver which was maximum on the fourth day after therapy; a decrease of splenic measurements from 21 to 14 cm. below the costal margin, and a decrease in liver measurements from 15 to 14 cm. This effect disappeared four weeks after therapy, at which time the spleen and liver were the same size as before treatment.

Intradermal 48/80,* 10 μg., was given into an area of skin involvement of the left forearm with an arterial tourniquet on the injected arm. There was an immediate whealing reaction at the injected site, 2 cm. in diameter, which persisted for ten minutes. There was also spontaneous whealing of the skin lesions of the injected arm below the level of the tourniquet and an accentuated reaction to stroking. A biopsy specimen of the injected skin site one hour after the administration of 48/80 revealed definite diminution of the number of mast cells in comparison to simultaneous skin biopsy obtained from a similarly involved area of the opposite arm.

The patient was given an intravenous injection of 200 μc. of $BaSO_3$-S^{35} with a total weight of 0.8 mg. as sulphur. After forty-eight hours, marrow aspiration and liver biopsy were performed for radioautography. Following development for eight weeks radioautographs revealed marking of the mast cells of bone marrow and liver. Marking of cells of the granulocytic series and of some parenchymal hepatic cells was also observed.

The patient's recent course has been for the most part asymptomatic. He was discharged from the hospital without further therapy. He has gained weight, but the skin changes and the hepatosplenomegaly have not changed. A postoperative incisional hernia was repaired without difficulty under general anesthesia in September 1958. He has developed chronic respiratory symptoms of tight cough and some exertional dyspnea associated with occasional findings of expiratory wheezes.

COMMENTS

This patient's pathologic disorder fulfills the criteria of urticaria pigmentosa, with skin lesions, many of which were pigmented, of at least ten years' duration. Stroking gave characteristic whealing limited to the lesions without involvement of intervening skin, and biopsy specimens showed massive mast cell infiltration.

Although fairly typical, these skin lesions were thought incidental by both internists and dermatologists when first seen and a diagnosis of alcoholic cirrhosis was offered to explain the hepatosplenomegaly. The benign course and normal liver functions led to further evaluation, at which time the skin lesions were recognized as urticaria pigmentosa. Biopsy specimens of the liver revealed no cirrhosis or fatty infiltration. Toluidine blue staining of the tissue sections revealed the systemic nature of his disease.

The difficulty in recognition of mast cell

* 48/80, a condensation product of formaldehyde with paramethoxy-phenyl-ethylamine, was obtained from Burroughs Wellcome and Co., Tuckahoe, New York.

infiltrations in routine histologic sections has been commented upon in several reports [*3,7–9*]. It seems possible that many of these patients are not being diagnosed due to the fact that proper metachromatic stains of skin and biopsy sections of the liver are not used.

In normal man the corium contains relatively few mast cells per microscopic field [*11*]. In a study of splenic imprints from patients with a number of diseases, mast cells occurred in only zero to 0.25 per cent of all nucleated cells [*12*]. Friedman et al. [*9*] also found insignificant numbers of mast cells in splenic sections from fifteen random examinations at autopsy. Ellis [*5*] studied the mast cell counts of various tissues of infants and found one or two per oil immersion field in the liver, lung, kidney, pancreas and urinary bladder. Examination of the bone marrow revealed no mast cells, and in a special search in tissues of patients with hepatic cirrhosis and Hodgkin's disease these cells were not found. Fadem [*13*] searched for mast cells in 2,800 marrows, both normal and diseased, and found them present in only seven cases, in which associated marrow depression was present. On the other hand, Williams [*14*] using particle smears obtained at biopsy, found mast cells in 17 per cent of 325 patients. Johnstone [*15*] was able to demonstrate mast cells in 70 per cent of bone marrow aspirates, and he was of the opinion that mast cells are a normal bone marrow constituent.

Splenomegaly has been a prominent feature of the more severe forms of systemic mast cell disease, and Friedman's patient [*9*] presented with acute splenic rupture. However, in a patient shown to have liver and bone marrow infiltration splenomegaly developed late in the course of the disease [*16*].

Roentgenographic studies of these patients have revealed bone lesions related to urticaria pigmentosa. Many of these patients have shown only a local calcified island or cystic lesion which may well have been incidental. However, generalized bone changes sometimes described as trabecular thickening or osteoporosis, but usually as osteosclerosis or stippling of ribs, skull and long bones occurred in many of the reported patients with systemic urticaria pigmentosa [*17–19*]. Osteosclerosis was observed in our patient. Mast cell infiltration has been found in bone marrow aspirates and biopsy specimens from these diffuse bone lesions, which seem to be due to invasion by these cells. Radiologic signs may be found without visceral enlargement [*20*], possibly as early evidence of systemic disease.

Though absent in our patient, mast cells have been reported in the peripheral blood of patients with mast cell disease [*3,21–23*]. In the patient reported on by Asboe-Hansen [*16a*], basophilia was reported. Such cases have been termed leukemia of the mast cell type, but only in Efrati's case [*23*] were the circulating mast cells characterized as immature.

Gastrointestinal complaints, particularly diarrhea, have been commonly reported in severe forms of the disease and in the patient reported on by Ellis [*5*] this apparently was a major factor in the child's death. One may infer that serotonin originating from mast cells may be responsible for this symptom. Our patient had a long history of vague pain in the upper part of the abdomen, but this seemed attributable to hiatal hernia. There was no diarrhea and no increase in serotonin metabolites was found in the urine even after administration of agents that destroy mast cells.

The evidence for heparin as a constituent of mast cells is based upon the good correlations of tissue levels of this substance with the number of mast cells, and the release of heparin into the circulation following injection of drugs which destroy mast cells [*25*]. However, Marx et al. [*10*] did not find agreement between mast cell and heparin content in tissues of various species. High levels of heparin-like substance were found in the tissues of patients with severe mast cell disease [*26*]. The peculiar basophilic staining properties of the cells have been attributed to heparin [*27*], although such staining is also given by sulfur-free mucopolysaccharides [*28*]. Graham et al. [*29*] have hypothesized that the basophilic staining heparin is attached to histamine and to protamine-type organic bases within the granules. However, Julen et al. [*30*] suggested that heparin is present in the form of an amorphous covering of the granules.

We were unable to demonstrate increased heparin-like substances in the blood-stream of the untreated patient. This is in accord with the findings of other workers [*3,16,28,31*]. Although the dog seems capable of releasing heparin into the blood-stream from liver mast cells under the effect of various chemical stimuli, this has not been observed in other species in which the heparin in mast cells does not seem to be released as a circulating anticoagulant [*32*]. How-

ever, Bolgert and Le Sound [*33*] and Degos et al. [*63*] reported on patients with urticaria pigmentosa in whom there were hemorrhagic tendencies and prolonged clotting times.

Urbach et al. [*34*] applied vigorous massage to the skin of eight patients with urticaria pigmentosa without systemic disease, thus providing sufficient trauma to degranulate mast cells, and observed significant prolongation of the clotting time in two patients, and increase of protamine-titratable heparinoid substances in six patients. We were unable to produce a detectable heparin level in the circulating blood after vigorous massage, but the clotting time and lipemia-clearing substance were transitorily increased following large doses of intravenously administered adrenal steroid. In a somewhat similar experiment Reilly et al. [*31*] found no change in the clotting time following administration of ACTH. Nitrogen mustard therapy was not followed by changes in the clotting time in our patient.

An explanation for the absence of circulating heparin following degranulation of the mast cells has been provided by Higginbotham and Dougherty [*35*], who found fibroblastic phagocytosis of free mast cell granules tagged with S^{35}, with formation of "pseudo-mast cells." The substances thus engorged may well be incorporated into connective tissue ground substances [*36*], without being released into the circulation.

The finding of hemorrhagic phenomena in the skin of patients with urticaria pigmentosa without increased clotting times [*11,37*] would also suggest that while there may be some anticoagulant release locally, the heparinoid substance does not enter the circulation. The hemorrhagic tendency of the patients recorded by Richer et al. [*28*] and by Waters and Lascon [*3*] was due to involvement of the liver with prothrombin deficiency, while the patient recorded by Brodeur and Gardner [*21*] had skin lesions closely resembling ecchymoses of hemorrhagic purpura associated with low platelet counts. Asboe-Hansen [*11*] has observed cutaneous hemorrhages in association with increased vascular fragility.

Enlargement of the liver has been reported with systemic mast cell disease and has been studied histologically in several cases. Diffuse mast cell infiltration, as observed in our case, has been described [*3,5,9,16,21*]. Cirrhotic changes also have appeared [*5*].

Berlin's patient [*38*] was found to have some distortion and destruction of liver cells without fibrosis, while Waters and Lascon's patient [*3*] had atrophy of liver cells thought to be due to pressure by mast cell infiltration. Liver functions were normal in our case, but alterations of functions may be present [*16*]. Of interest is the statement of Bloom [*39*] that in dogs with mast cell tumors cirrhotic changes develop.

Histamine has been found in high concentrations in human and animal tissues rich in mast cells [*26,27*]. We were not successful in demonstrating increased circulating levels of histamine in the serum of our patient either in the untreated stage or after the administration of nitrogen mustard or adrenosteroid therapy. Brogren et al. [*20*] have recently reported high concentrations of histamine in the urine of patients with urticaria pigmentosa without known visceral involvement, but with diffuse bone changes in some instances. One of these patients demonstrated a marked rise in levels of urinary histamine following stroking of the lesion. Although histamine is rapidly excreted by the kidneys [*27*], it is also bound and detoxified by tissues [*60–62*], and this possibly accounts for our failure to identify it.

Serotonin (5-hydroxytryptamine) has been identified as a mast cell constituent in the mouse [*41–43*] and rat [*44*], but was not found in dog mast cell tumors [*45*]. Several reports indicate normal 5 hydroxyindoleacetic acid excretion in patients with urticaria pigmentosa [*20,28,43*] and this was found to be normal in our case. Serotonin was not increased in the mast cell rich tissue from patients [*26,43*], indicating a true difference in species.

Brodeur and Gardner [*21*] postulated the mast cells to be storage centers for histamine and heparin, in association with inadequate breakdown of these substances. In this regard the administration of heparin has been shown to increase the number and granulation of mast cells in the mesentery of the rat [*45*].

There is experimental evidence to indicate that mast cells incorporate sulfate from the ground substance [*45a*] but the mucopolysaccharide which the cells release physiologically is sulfur-free and susceptible to hyaluronidase [*49*]. No studies on the release of hyaluronic acid from the mast cells have been performed in the present case.

Mast cells are susceptible to a large number of unrelated substances which disrupt or degranulate mast cells *in vitro* and *in vivo*, suggesting

unusual fragility of the cell membrane. These substances include distilled water [*2*], ACTH [*45*], Tyrode's solution, and saline solution [*49*]. Nitrogen mustard and x-radiation [*45*] are also potent mast cell disrupters. The compound, 48/80, a condensation product of formaldehyde with paramethoxy-phenyl-ethylamine, even in small concentrations causes degranulation of mast cells *in vivo*, and release of histamine without cell disruption [*2,40*]; larger doses cause mast cell disruption. Such agents might be considered of value in the treatment of mast cell disease.

The administration of cortisone has been found to be a potent degranulator of mast cells in man [*46*], and mast cell tumors in dogs regressed under cortisone therapy [*47*]. Although Robbins [*48*] reported good results with ACTH gel in bullous mast cell infiltration of the skin of a child, others have observed no benefit following cortisone or ACTH therapy [*8,37*]. Our patient showed little clinical response to either intravenous or orally administered hydrocortisone medication for a ten day period, although after a single large dose some heparin release seemed to occur. Urbach et al. [*50*] considered that desoxycorticosterone acetate (DOCA) had some effect, which developed slowly, in the treatment of urticaria pigmentosa of children.

Nitrogen mustard therapy has been described as a potent agent for degranulating and disrupting mast cells [*4,45*] but to our knowledge has not been previously used in the treatment of systemic mast cell disease. The transient response in our patient, as demonstrated by diminution in the size of the liver and spleen, may be due to destruction followed by a period of regeneration of mast cell infiltrations.

The possibility of treating this disease with radioactive sulfate (S^{35}) was considered, since skin mast cells exhibit a high uptake of this substance [*51*], presumably due to their high mucopolysaccharide content [*52*]. Radioautographs of liver sections showed mast cell uptake of S^{35} in our patient after tracer doses. Therapeutic doses were not used in view of the patient's satisfactory clinical status and the risks involved, but might be considered in therapy of this disease.

The effect of intradermal 48/80 administered into the forearm of our patient with an arterial tourniquet suggested histamine release at the site of injections, as evidenced by local whealing as well as a flare of lesions of the entire area distal to the tourniquet. Experience in human subjects with this agent being limited [*53*], large doses were not given since severe reactions might have been elicited by histamine liberation.

X-ray therapy might give a response [*22*] but in this type of disseminated disease, extensive involvement makes this of little practical value. For the more localized types of mast cell disease radiation might be effective.

Association of urticaria pigmentosa and salicylate sensitivity has been reported [*20,54,55*], suggesting salicylates to be histamine liberators. No indication of salicylate sensitivity appeared in the history of our patient.

The development of pulmonary symptoms in our patient might possibly be related to chronic histamine and/or serotonin effect.

SUMMARY

A case of systemic mast cell disease, a rare cause of unexplained hepatic and splenic enlargement, is presented. Although associated with urticaria pigmentosa, the significance of the skin lesions may be easily overlooked. Routine tissue sections may not allow recognition of mast cell infiltration; special stains are necessary when this condition is suspected.

Definite but temporary improvement followed nitrogen mustard therapy, and no untoward pharmacologic reactions were seen. No histaminemia or increase in excretion of serotonin metabolites occurred during treatment. No histaminuria was noted. Hydrocortisone and prednisone therapy produced no clinical improvement, although heparinemia following large intravenous doses of hydrocortisone indicated mast cell degranulation or destruction.

Tracer doses of S^{35} were incorporated into mast cells as shown by radioautography. Its possible use in therapy has been considered, but rejected in this case because of potential risks to a patient whose clinical status was satisfactory.

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Central Pontine Myelinolysis*

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ADAMS, Victor and Mancall [1] recently described a distinct and previously unrecognized disease entity which they termed central pontine myelinolysis. In this condition there is an isolated area of myelin destruction with relative preservation of nerve fibers in the central portion of the pons. This was associated, in two patients they described, with a fulminating clinical picture developing as a sudden change in the course of a chronic debilitating disease. These patients died within a few days. The lesions in the other two patients were small and could not be correlated with clinical findings. The antecedent conditions in the four patients were chronic alcoholism (three cases) and scleroderma with nutritional deficiency (one case).

Because the possible variants of this condition are as yet unexplored, an extensively studied example is reported in detail. The antecedent disease was an infection of the frontal sinus with localized spread in the form of a subdural abscess over one frontal lobe; this was four weeks in duration. The episode associated with the pontine lesion at first resembled acute psychosis and, a few hours later, encephalitis. Some further data on the pathology of central pontine myelinolysis are also provided.

CASE REPORT

A twenty-eight year old white woman was admitted to the Knickerbocker Hospital on November 17, 1958, because of severe headache and changes in behavior. Her present illness began three days before admission with the abrupt onset of a severe headache which could not be relieved by the ingestion of salicylates. For the preceding four weeks she had had symptoms of an infection of the upper respiratory tract which did not incapacitate her but which persisted. She continued to work during this period without interruption. Three days prior to admission she had a severe frontal headache and pain in the supraorbital region accompanied by general malaise and chills. On the following day she became disoriented and demonstrated unusual aggressive behavior. A physician found the patient to be febrile and uncooperative. A diagnosis of viral pneumonitis was made and Achromycin,® 250 mg. four times a day, was prescribed. Later that day she appeared to be markedly improved; her temperature continued to be within normal limits; her behavior was completely normal and she fulfilled a social obligation that evening. The day preceding admission she complained once more of frontal headache and malaise, but continued afebrile. Her behavior was normal. She continued to take Achromycin and added salicylates to her medication for headache without apparent effect. The evening prior to admission she became restless, and aggressive behavior patterns again appeared.

On admission, physical examination disclosed a robust young woman, acutely ill, with a temperature of 102°F., respirations 18 and blood pressure 110/70 mm. Hg. She appeared morose, sporadically aggressive, refused examination and was either unable or unwilling to give coordinated sequential information about her illness. Her affect was disturbed and her behavior suggested an acute schizoid reaction. There were no abnormal reflexes, no nuchal rigidity, and ocular movements were normal. Initial laboratory study showed a leukocytosis of 19,250 per cu. mm. with 77 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes, and 2 per cent monocytes. A roentgenogram of the chest revealed no abnormalities. The tentative diagnosis of viral encephalitis was made, and treatment with salicylates and oral fluids was begun. The patient continued lethargic and uncooperative with considerable loss of memory. Neurologic examination, however, remained within normal limits except for the clouded sensorium. Consent for lumbar puncture could not be obtained until the third hospital day. The initial pressure was 290 mm., final pressure 170 mm. with normal dynamics. The spinal fluid contained 350 cells per cu. mm., predominantly lymphocytes; the protein was 140 mg., glucose 70 mg., chlorides 770 mg. No organism was seen on smear, but a few colonies of nonhemolytic streptococcus grew on one of three culture plates. The possibility that this was a contaminant was considered, and on the fifth hospital day examination of the spinal fluid was repeated. The manometric values were unchanged. The fluid contained 420 cells,

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predominantly lymphocytes; the protein was again 140 mg., the glucose again 70 mg., and the chlorides 608 mg. No organism was seen on smear, and this culture was sterile.

During the first five hospital days the patient's condition remained unchanged; confusion and lethargy persisted. There was no stiffness of the neck or any motor or sensory deficit. The temperature oscillated between 101° and 103°F. A second white blood cell count disclosed 12,250 cells per cu. mm. with 80 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, and 2 per cent monocytes. The erythrocyte sedimentation rate was 120 mm. per hour. Results of febrile agglutination tests were negative. The reaction to a cold agglutination test was positive at 1:4 and a heterophil agglutination test also was positive at 1:4. The blood non-protein nitrogen was 28 mg. per 100 ml., the fasting blood sugar 107 mg., and the antistreptolysin O titer was 166 units. Non-hemolytic Staphylococcus aureus was grown on throat culture. A blood culture was negative. Achromycin, 1 gm. daily in divided doses, was given and continued for the remainder of her hospital course.

During the next few days the patient's condition deteriorated progressively. Lethargy became more profound. Although there was no difficulty in swallowing, fluids had to be administered intravenously and food by gastric tube. Six days after admission slight nuchal rigidity was noticed and a positive Brudzinski sign appeared. Administration of ACTH in full dosage was begun and continued for the remainder of her hospital course. A spinal tap on the seventh hospital day revealed clear fluid with normal pressure and dynamics, containing 60 cells per cu. mm., all lymphocytes. The protein had fallen to 49 mg. per 100 ml., glucose 72 mg., chlorides 758 mg. No organisms were found on smear or culture. Viral cultures of this fluid were negative. Viral complement fixation studies were negative for lymphocytic choriomeningitis, western equine encephalitis, eastern equine encephalitis, St. Louis encephalitis, mumps, poliomyelitis and the A, B and Japanese strains of influenza virus. The white cell count rose to 21,000 per cu. mm. with 74 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes and 8 per cent monocytes. Agglutination studies were repeated, showing typhoid O positive at 1:80, typhoid H positive at 1:40, paratyphoid A and B negative, Brucella abortus positive at 1:160, and proteus OX-19 positive at 1:80. Stool culture was negative for ECHO virus. Urinary retention developed on the eighth hospital day. Later that day, lethargy deepened into stupor. The eyes became widely dilated and fixed in the midline, not deviating with movements of the head. The right pupil responded sluggishly to light and the left pupil was fixed. The optic discs were well outlined and there was no evidence of papilledema. Nuchal rigidity seemed more pronounced; corneal and gag reflexes were absent; superficial and deep tendon reflexes were present and symmetrical. No abnormal reflex was present.

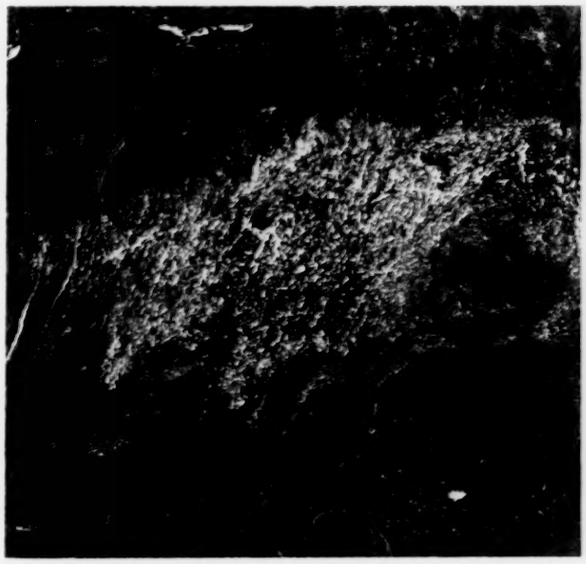


FIG. 1. A portion of the pontine lesion. Silver carbonate stain for nerve fibers × 15. Note the sharp although somewhat irregular edges of the lesion. There is no cavitation.

On the ninth hospital day the patient was semicomatose. Nuchal rigidity was obvious and Brudzinski's sign positive. The remainder of her neurologic status was as it had been the day before. A fourth spinal tap was performed, revealing an initial pressure of 400 mm., final pressure 250 mm., normal dynamics, 48 cells (all lymphocytes), protein 56 mg. per 100 ml., glucose 64 mg. and chlorides 740 mg. No organism was seen on smear and the culture was sterile. The patient was comatose on the tenth hospital day. Cheyne-Stokes respiration supervened. She suddenly became cyanotic and stopped breathing. Although an emergency tracheotomy was performed and intracardiac epinephrine was administered, the patient died.

At necropsy, apart from moderate pulmonary congestion and edema the pathologic processes were confined to the cranium and its contents. The left frontal sinus was filled with purulent material from which non-hemolytic streptococci were readily demonstrable by smear and culture. On opening the calvarium, the dura over the left cerebral hemisphere was edematous and congested. After reflection of the dura a well circumscribed abscess was found in the subdural space over the left frontal pole and the anterior portion of the convexity of the left frontal lobe. It contained about 40 cc. of purulent material from which non-hemolytic streptococci were cultured. The remainder of the left cerebral hemisphere, the entire right hemisphere and the base of the brain were entirely free from exudate and other changes. The brain weighed 1,550 gm.

Multiple sections through the brain showed no

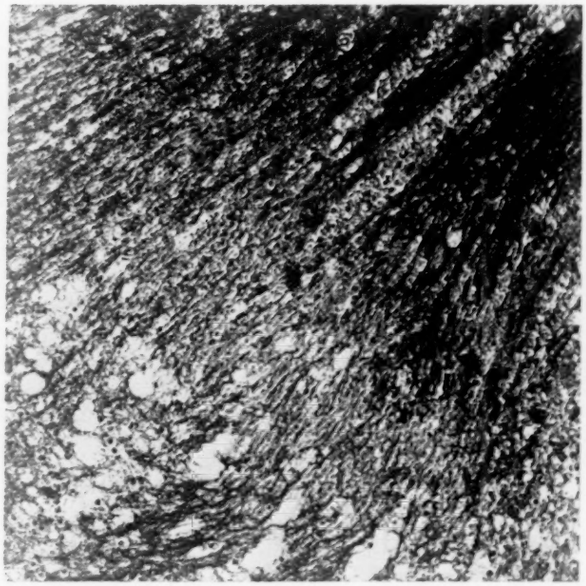


FIG. 2. Abrupt loss of myelin staining at the edge of the lesion. Weil's method × 150.

evidence of intracerebral abscess or other lesions except in the pons, where there was a small linear streak of recent hemorrhage 4 by 1 mm. just to the left of the midline. No conspicuous gross alterations were seen in the rest of the pons.

Many blocks were taken from all parts of the brain. Except in the region of the subdural abscess, the meninges were normal and there was no extension of the inflammatory process into the cerebral cortex proper in the region of the abscess. The architecture of the cerebral hemispheres and cerebellum was normal in appearance, except for slight edema. A careful survey of the brain failed to show any evidence of myelin destruction or other degenerative lesion except in the pons.

The *pontine lesion* was located in the center of the rostral portion of the basis pontis, with the hemorrhage recognized grossly lying to the left of its center. The diameter of the lesion was 11 mm., measured in paraffin section. The lesion consisted of a single, symmetric area of myelin loss but with relative preservation of nerve fibers. On very low power microscopic examination, the tissue in the focus appeared much rarefied (Fig. 1), but this was the result of almost complete dissolution of the myelin sheaths. Staining of the myelin sheaths by Weil's method ceased abruptly at the margin of the lesion (Fig. 2); only in rare instances could even a single fiber with preserved sheath be found within the focus. The edges of the lesion were sharp but somewhat irregular. (Fig. 1.) The nerve fibers, however, continued through the lesion without interruption. (Fig. 3.) Within the focus the nerve fibers took the silver carbonate intensely; there was little certain evidence of fragmentation but it is possible that a few fibers



FIG. 3. Relative preservation of nerve fibers in the lesion. The uninvolved pons is at the top and the junction with the lesion is marked by the zone of swollen myelin sheaths. Silver carbonate stain for nerve fibers × 150.

may have dropped out entirely. At the edge of the lesion, at the point where the Weil staining stopped, the myelin sheaths were greatly swollen in a sharp band. (Fig. 3.) This change in staining was uniformly present wherever the lesion abutted upon the unaffected tissue of the pons.

Within the focus, oligodendroglia were identified only as small, darkly stained masses. No oligodendroglia of normal morphology were found, whereas outside the focus these cells and other glia had their usual appearance. There was no evidence of astrocytic reaction within or adjacent to the focus. Total absence of gitter cell formation or other types of reactive cell change was a notable part of the histologic picture.

The small hemorrhage noted on gross examination consisted of well preserved blood cells and was regarded as very recent or agonal. Considerable capillary congestion was present within the lesion and elsewhere in the pons. Arteries in the lesion, in the rest

of the pons and in other portions of the brain were free from sclerosis.

The pons outside the lesion was composed of nuclei and fiber tracts in normal pattern. The nerve cells showed no regressive changes in any portion.

COMMENTS

In reporting four cases of central pontine myelinolysis, Adams, Victor and Mancall [*1*] clearly established a previously unrecognized disease entity with definite clinicopathologic correlations. The findings in the patient just described are fully in accord with their description and present some additional information on the condition.

The pathologic change is a single, symmetric focus of myelin destruction with relative preservation of nerve fibers. This develops in the same location in each patient, namely, at the center of the basis pontis. It spreads out centrifugally, remaining symmetric even when most of the pons is involved [*1*]. At the advancing edge of the lesion the myelin sheaths are strikingly swollen (Fig. 3), while those of the pons outside the lesion stain normally. For this process the term "myelinolysis" seems precise and appropriate. It is difficult to think of a lesion in any other disease developing in just this way. These facts make central pontine myelinolysis significant in the general study of degenerative disorders of the central nervous system. Perhaps Marchiafava-Bignami's disease is the nearest counterpart [*1*]. Adams et al. [*1*] have cogently commented on the comparison which they made because of "its symmetry and more or less demyelinative character. This disease is characterized by a symmetric degeneration of myelin and, to a less extent, of axis cylinders, sometimes progressing to cavitation. The corpus callosum is most frequently affected, and less often the central parts of the anterior commissure, the central and convolutional cerebral white matter, the optic chiasm and radiations, and the middle cerebellar peduncles . . . From the histologic point of view the lesions in our cases bear a close resemblance to those of Marchiafava-Bignami's disease. In both the lesions are symmetric; there is relatively greater destruction of myelin than of other tissue elements, and no clear relationship of the lesions to blood vessels is evident; also inflammatory cells are not prominent. The analogy between the two processes cannot be carried further, however, because of the contrasting location of the lesions. In none of the reported cases of Marchiafava-Bignami's disease have pontine lesions been described, and none of our cases showed any change in the regions characteristically affected in Marchiafava-Bignami's disease. Furthermore, in our cases all fiber systems were indiscriminately affected, so that the disease could not be regarded as systematized."

The clinical syndrome in the patient just described is also in accord with that described by Adams et al. [*1*]. In all instances there has been a preceding debilitating disease. Some but not all reported cases have been associated with alcoholism, of which there was no evidence in the present patient. Suddenly, an abrupt change occurs; a fulminating picture of central nervous system involvement appears with death occurring ten days to three weeks after the onset of the acute episode. If the lesion is large enough to involve many important pontine pathways, there may be pseudobulbar phenomena, and quadriplegia if the corticospinal tract becomes involved (Cases 1 and 2 [*1*]). With smaller foci, the clinical picture may be suggestive of viral encephalitis, as in the case reported here. The histology and anatomic site are clearly not those expected in lesions due to an infectious agent. The negative results of extensive viral studies in the present case are further evidence against a viral etiology.

Another condition which might be considered in clinical differential diagnosis is acute, fulminating multiple sclerosis. A few instances have been reported [*2,3*] in which the time interval from onset of symptoms to death is similar to that in central pontine myelinolysis. However, the localizing signs, when present, are not confined to those associated with pontine involvement. The morphologic findings of multiple plaques in acute multiple sclerosis and the detailed histology of the lesions indicate that the two diseases are distinct.

Whether any form of allergic involvement of the central nervous system can produce a similar clinical picture is uncertain. The lesion bears no histologic resemblance to allergic encephalomyelitis. Likewise, there is no pathologic evidence of vascular origin.

The facts which seem to emerge regarding central pontine myelinolysis are its occurrence in patients suffering from a debilitating disease of diverse character; its fulminant clinical picture with fatal prognosis; the specific localiza-

tion of the lesion in the center of the pons; the relative preservation of nerve fibers and almost complete destruction of myelin sheaths within the focus; the absence of cellular response to the degenerated myelin. Further investigation is needed to determine how these are linked together.

SUMMARY

Central pontine myelinolysis is a recently recognized clinical and pathologic entity. The lesion is a solitary focus of myelin destruction with relative preservation of nerve fibers, located symmetrically in the center of the pons. It occurs in patients who have previously had a debilitating disease. The development of the pontine lesion is accompanied by the appearance of a fulminating picture of central nervous system involvement and death in ten days to three weeks.

A patient with this condition is described in detail. The antecedent illness was an extensive frontal sinusitis with subdural and intradural abscess. Death followed thirteen days after the onset of an acute episode which suggested viral encephalitis. The lesion was similar to those described in previously reported cases [*1*].

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3. Bailey, O. T. Discussion on demyelinating diseases. *Proc. First Internat. Cong. Neuropath.*, 1: 234, 1952.

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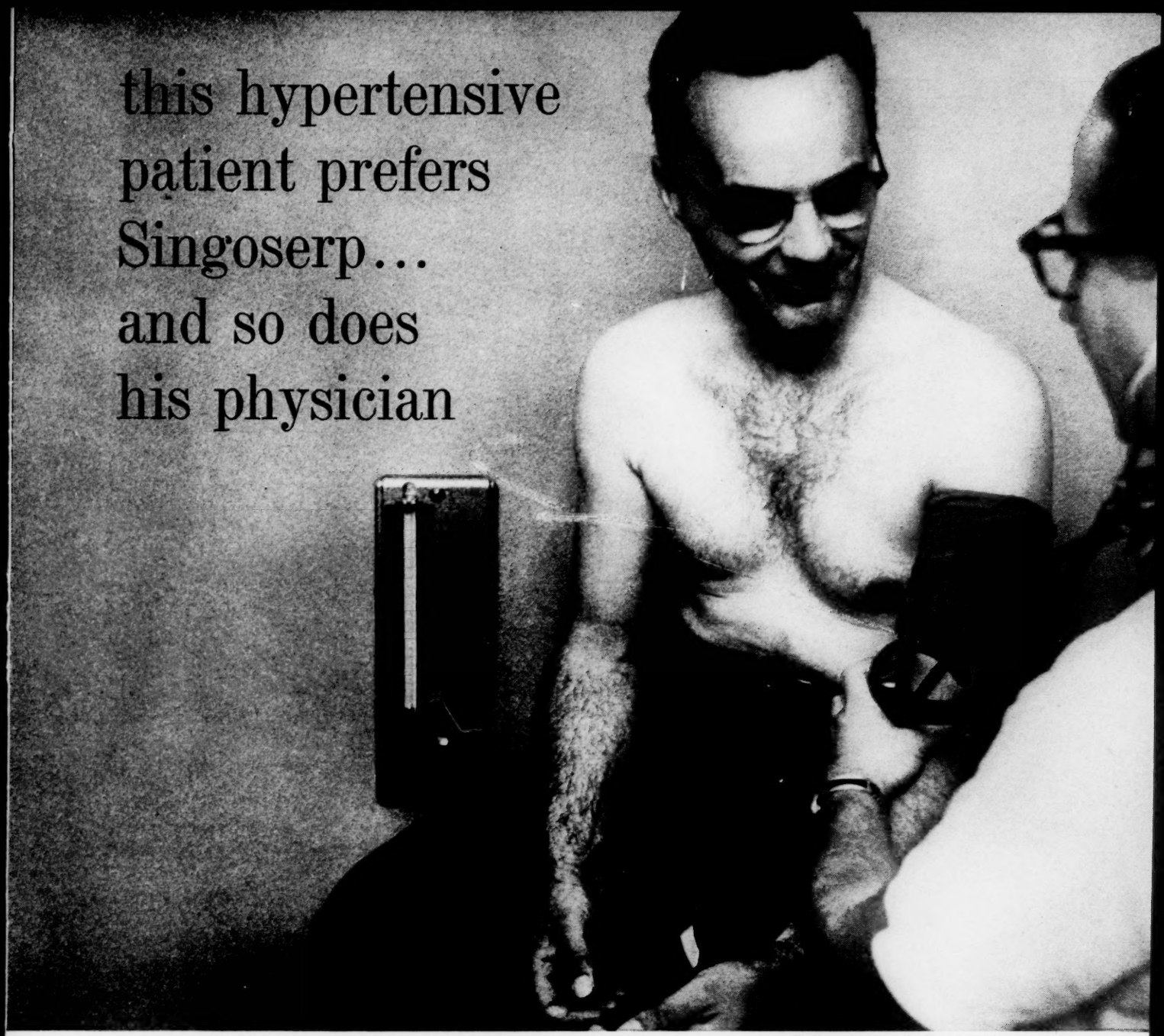


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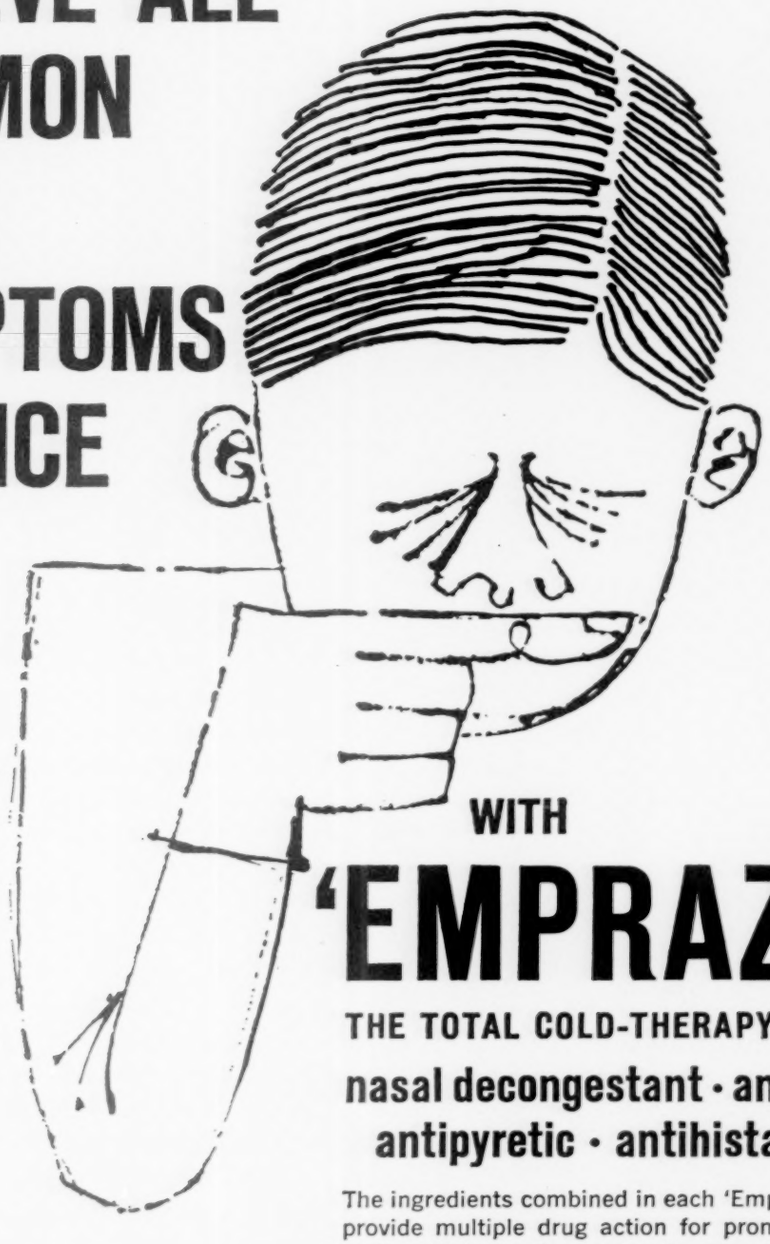
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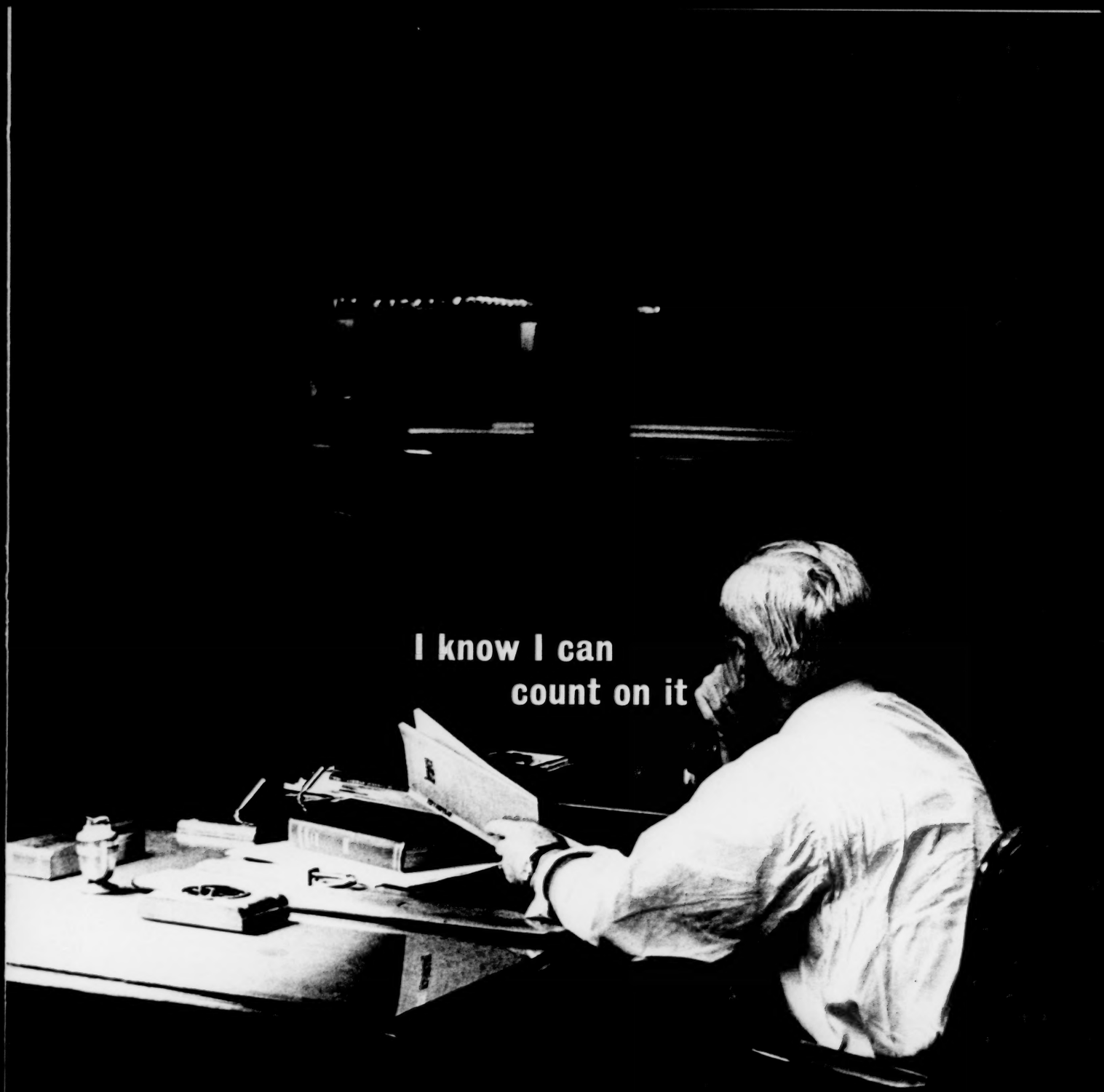
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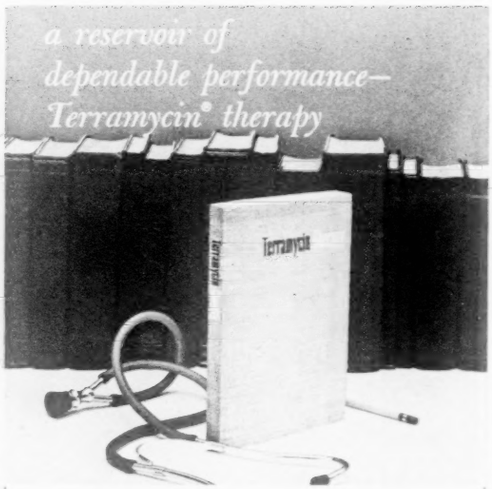
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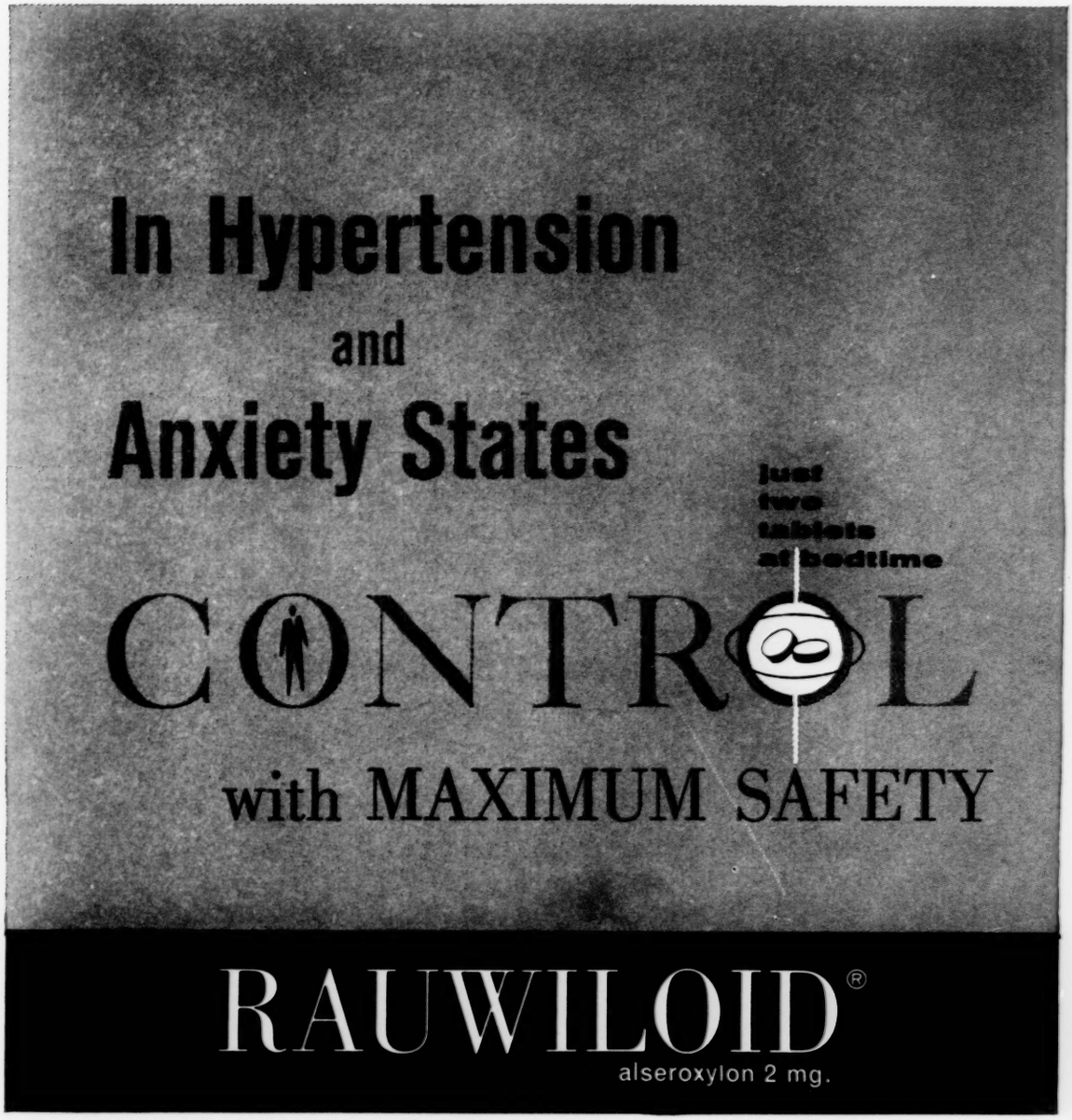
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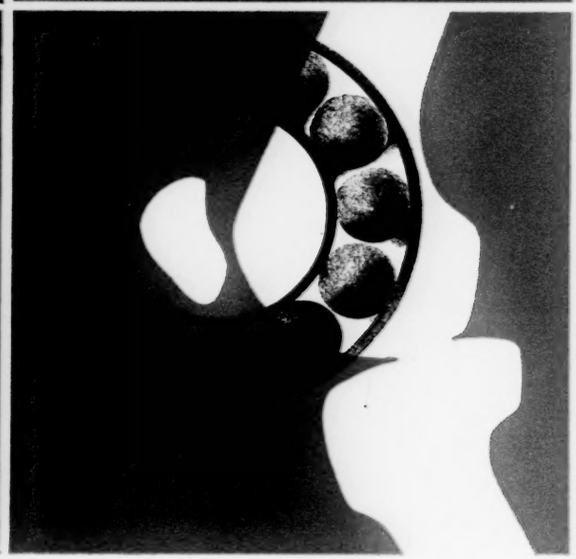
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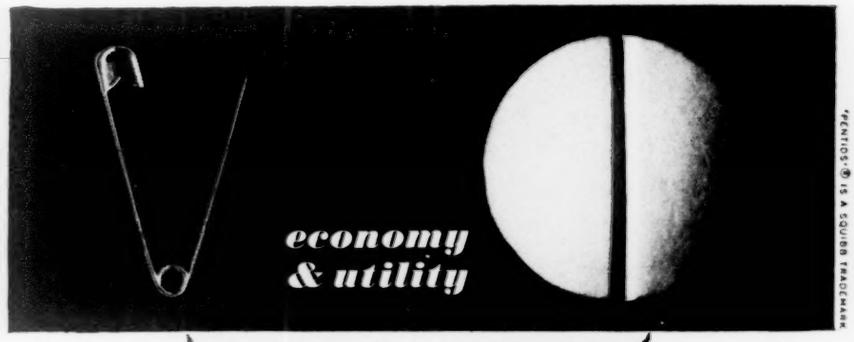
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in premenstrual tension



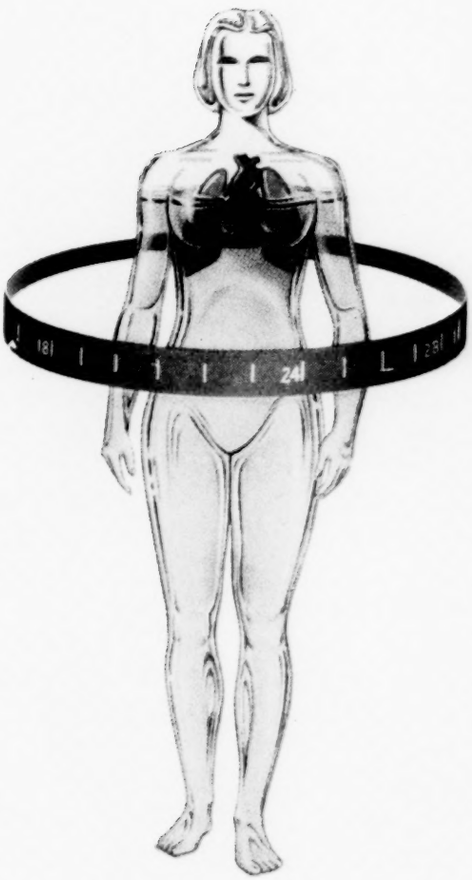
clinicians report rapid relief with

HYDRODIURIL®

HYDROCHLOROTHIAZIDE

increased potency–without corresponding increase in side effects

Fuchs, M. and Moyer, J.:
Diseases of the Chest 35:314, (March) 1959.



"Premenstrual edema is present in 40% of women and...consists of weight gain, subcutaneous edema, emotional lability, breast turgidity, anxiety and tension." In addition to controlling the objective symptoms of premenstrual tension, HYDRODIURIL may afford relief of subjective complaints including tension, nervousness and headache.

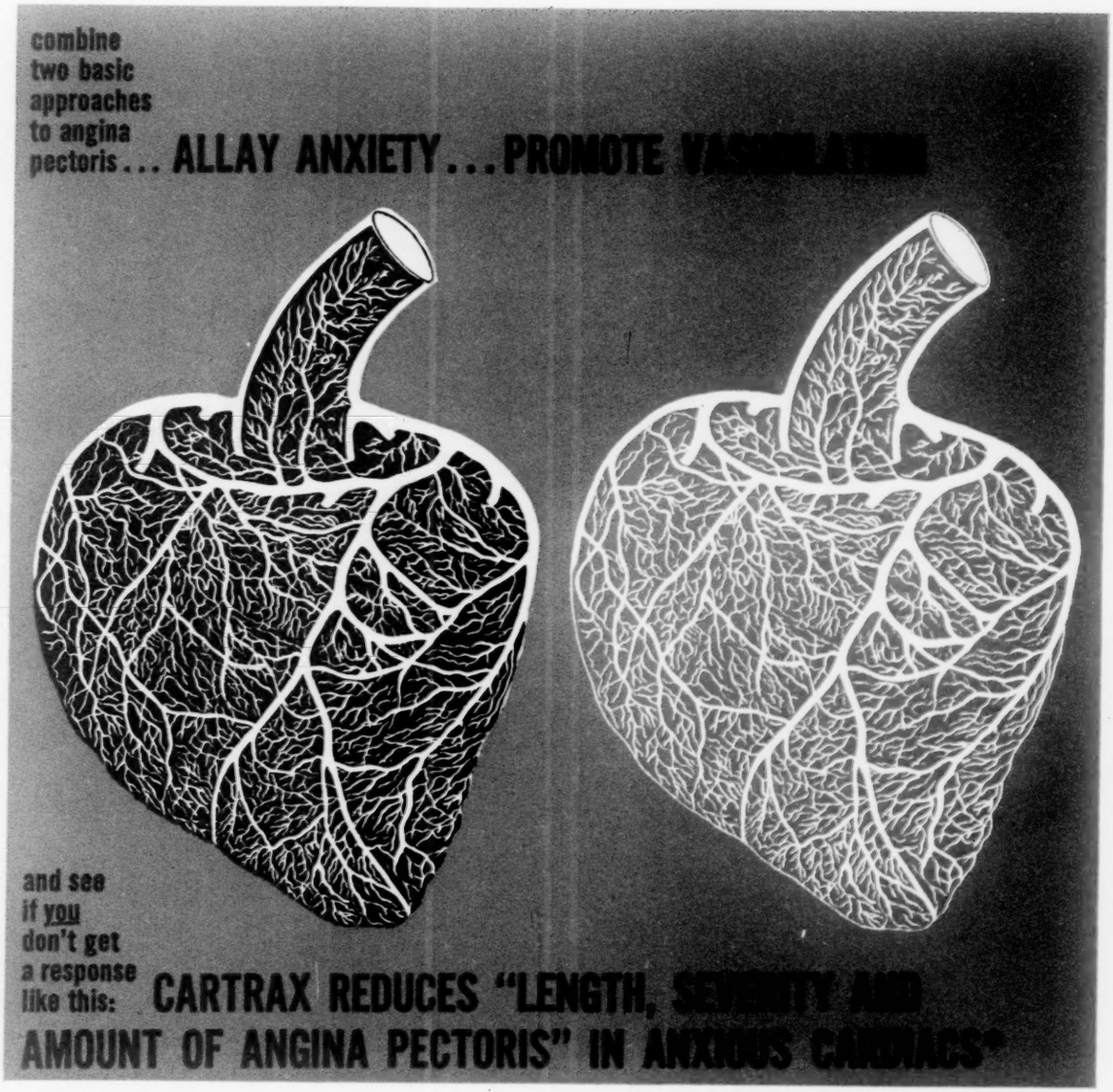
DOSAGE: 25 to 50 mg. of HYDRODIURIL once or twice a day, beginning the first morning of symptoms and continuing until the onset of the menses.

SUPPLIED: 25 and 50 mg. scored tablets HYDRODIURIL (hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request.

MSD MERCK SHARP & DOHME
Division of Merck & Co., INC. West Point, Pa.



Clark treated 31 anginal patients who showed signs of anxiety, fear, excitement and other forms of emotional stress. On CARTRAX, all 31 fared better than they had on previous therapy . . . as judged both by subjective reports and by reduced nitroglycerin requirements.*

CARTRAX combines PETN (for prolonged vasodilation) with ATARAX (the tranquilizer preferred for angina patients because of its safety and mild antiarrhythmic properties). Thus, CARTRAX helps you to cope with both components of angina pectoris—circulatory **and** emotional.

For a better way to help your angina patients relax, prescribe CARTRAX.

*Clark, T. E., in press.

CARTRAX®

PETN†+ATARAX®†† **Dosage:** Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. For dosage flexibility, CARTRAX "20" (pink) tablets (20 mg. PETN plus 10 mg. ATARAX) may be utilized at a level of one tablet three to four times a day. The tablets should be administered before meals for optimal response. For convenience, write "CARTRAX 10" or "CARTRAX 20." As with all nitrates, use with caution in glaucoma. **Supplied:** In bottles of 100. Prescription only.

† pentaerythritol tetranitrate †† brand of hydroxyzine

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being™



sprained wrist

Analgesics alone merely mask pain. New Medaprin adds Medrol* to suppress the inflammation that *causes* the pain and stiffness. Thus, to the direct relief of musculoskeletal pain,

Medaprin*

adds restoration of function.

Medaprin is supplied in bottles of 100 and 500 tablets.

Each tablet contains:

Medrol (methylprednisolone)	1 mg.
Acetylsalicylic Acid	300 mg. (5 grs.)
Calcium Carbonate	200 mg.

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

Upjohn

*Trademark, Reg. U. S. Pat. Off.

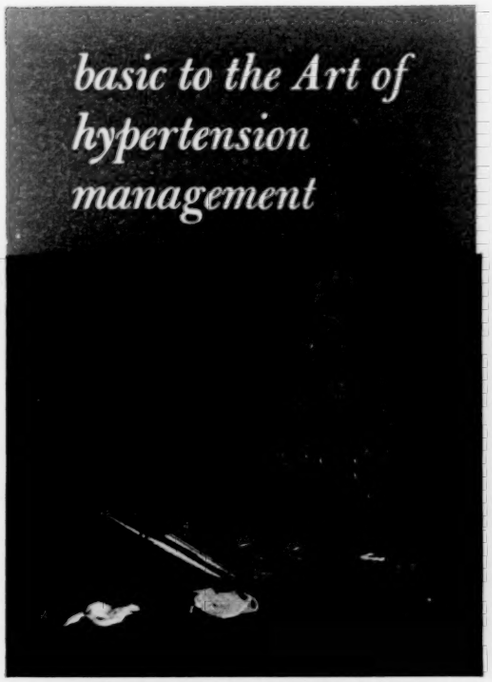


BAD DIGESTION INCLINES ONE TO SKEPTICISM, INCREDULITY, BREEDS BLACK FANCIES AND THOUGHTS OF DEATH JOSEPH CONRAD

When bad digestion is the consequence of digestive enzyme deficiency, Entozyme may dispel dreary symptoms such as pyrosis, flatulence, belching, and nausea, for it is a natural supplement to digestive enzymes. It provides components with digestive enzyme activity: **Pepsin,** N. F., 250 mg., **Pancreatin,** N. F., 300 mg., and **Bile Salts,** 150 mg. Because Entozyme is actually a tablet-within-a-tablet, these components are freed in the physiological areas where they occur naturally. Entozyme has proved useful in relieving many symptoms associated with cholecystitis, post-cholecystectomy syndrome, sub-total gastrectomy, pancreatitis, infectious hepatitis, and a variety of metabolic diseases.

A. H. ROBINS CO., INC. · RICHMOND 20, VA.

ENTOZYME®



moderil®
brand of rescinnamine
a refinement in rauwolfia alkaloid therapy

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

MODERIL is rescinnamine, a purified rauwolfia alkaloid providing the benefits of reserpine with reduced frequency and/or severity of certain reserpine side effects. Rauwolfia has been referred to as the first agent to be tried and the last omitted in antihypertensive therapy. When MODERIL is given with other antihypertensive agents, the latter may often be administered in lower dosage with fewer undesired reactions.

INDICATIONS: Primary therapy in mild to moderate labile hypertension. In more severe cases, as adjunctive therapy with other agents.

ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with MODERIL, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on *Rauwolfia* compounds who undergo surgery with general or spinal anesthesia. It is suggested that MODERIL be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, MODERIL should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

More detailed professional information available on request.

contain
the
bacteria-prone
cold

Tain

(Triacetyloleandomycin, Triaminic® and Calurin®)



inner
protection
with...

safe antibiosis

Triacetyloleandomycin, equivalent to oleandomycin 125 mg. This is the URI antibiotic, clinically effective against certain antibiotic-resistant organisms.

fast decongestion

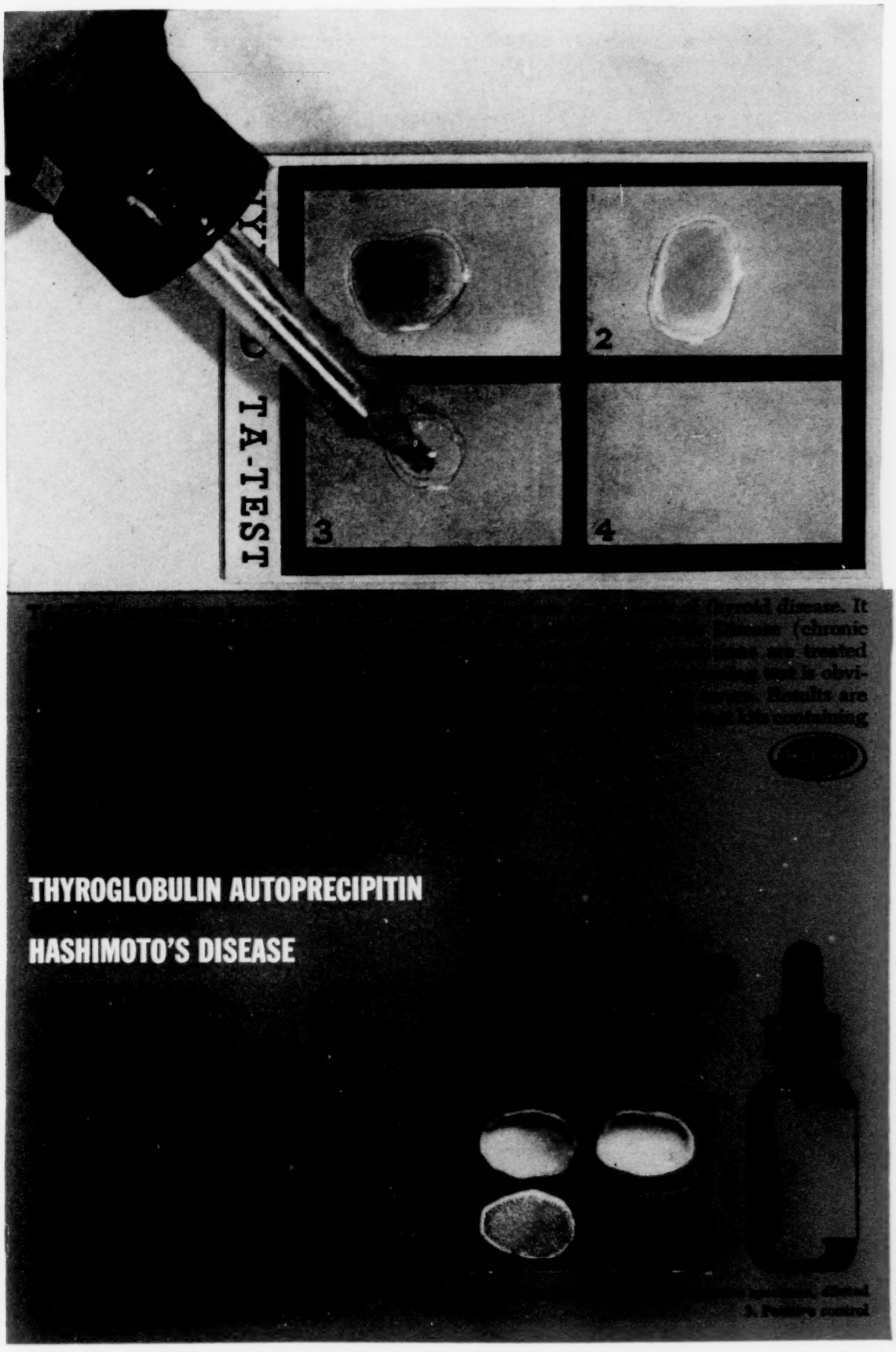
Triaminic®, 25 mg., three active components stop running noses. Relief starts in minutes, lasts for hours.

well-tolerated analgesia

Calurin®, calcium acetylsalicylate carbamide equivalent to aspirin 300 mg. This is the freely-soluble calcium aspirin that minimizes local irritation, chemical erosion, gastric damage. High, fast blood levels.

TAIN brings quick, symptomatic relief of the common cold (malaise, headache, muscular cramps, aches and pains) especially when susceptible organisms are likely to cause secondary infection. Usual adult dose is 2 Inlay-Tabs, q.i.d. In bottles of 50. ℞ only. Remember, to contain the bacteria-prone cold...TAIN.

SMITH-DORSEY • Lincoln, Nebraska
a division of The Wander Company


TEST
2
3
4
THYROGLOBULIN AUTOPRECIPITIN
HASHIMOTO'S DISEASE

You can–and should–adjust dosage with Orinase just as you do with insulin

Prescribe enough Orinase to release enough native insulin

A slight upward adjustment of Orinase dosage is often the only step needed to establish or regain optimum control of diabetes. The increase serves to make available the amount of Orinase-released native insulin *required* by the patient. The change may be made freely, to 3 grams or more a day, because Orinase has virtually no "ceiling" imposed on dosage by toxicity or untoward effects.

To maintain smooth control, to avoid needless "secondary failures," give sufficient Orinase to meet the varying needs of different patients or the varying needs of an individual patient.

1. CASE DATA COURTESY HENRY DOLGER, M.D.

EACH TABLET CONTAINS:
TOLBUTAMIDE . . . . . 0.5 GM.
*Trademark, Reg. U.S. Pat. Off.—tolbutamide, Upjohn

Orinase (grams/day)

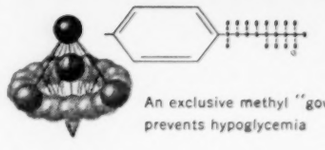
6/12/57	2.0
8/7/57	1.0
10/2/57	1.0
11/29/57	1.0
1/17/58	3.0
2/14/58	3.0
3/28/58	2.0
5/5/58	1.5

Actual doses used to maintain optimum control in patient J.S., male, age 54[1]

THE UPJOHN COMPANY,
KALAMAZOO, MICHIGAN

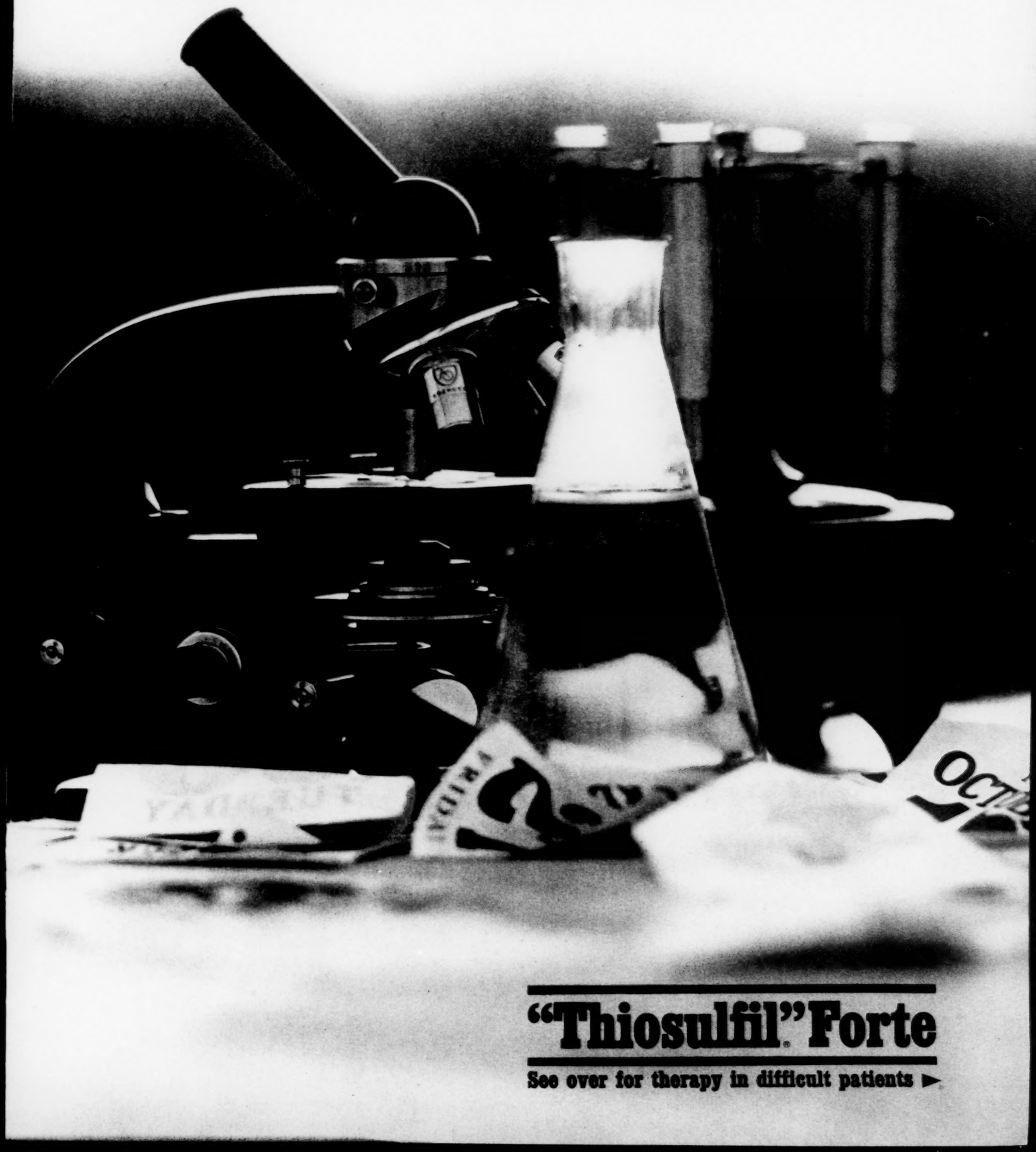
Upjohn

Orinase*



An exclusive methyl "governor" prevents hypoglycemia

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY-WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.



"Thiosulfil" Forte

See over for therapy in difficult patients ►

HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

RECORD OF SAFETY

In clinical studies of over 3,600 patients, the number of reactions, none serious, was less than 2 per cent.[1-6] " 'Thiosulfil' was remarkably well tolerated, there being no discontinuation of treatment due to untoward effects, and very few mild reactions were noted."[2] "The drug can be taken over a long period of time with practically no untoward side reactions."[3] "Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not."[4] Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.[1] NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

PROOF OF EFFECTIVENESS

A review of more than 3,600 reported cases on "Thiosulfil" demonstrates: a) adequate drug dosage can be simply and economically achieved with a minimum incidence of complicating side effects; b) the antibacterial agent can be given over longer periods of time, particularly in cases involving urinary stasis.

Specific For Urinary Tract Infections: "Thiosulfil" reaches greater urinary concentrations in the active, free, nonmetabolized form than any other sulfa, single or mixed. "Thiosulfil" is rapidly excreted; as much as 79% of the drug is found in the urine after eight hours—of this, 98% is in the active form.[5] The entire g.u. tract is, thus, subjected to continual "sulfa baths" of active drug—more wide spectrum antibacterial activity at site of infection.

Even where urinary stasis exists and cannot be readily corrected, prolonged or even indefinite use of "Thiosulfil" on a reduced dosage schedule will usually keep the infection under control, patients comfortable, and side effects minimal. "Thiosulfil" may materially reduce the likelihood of infections ascending to the parenchyma of the kidneys and subsequent serious systemic involvement.

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day[1]
2 weeks to 3 months	2 Gm./day[2, 6]
3 months or longer	0.5 Gm./day[7]

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed.

Supplied: No. 786: Each tablet contains 0.5 Gm. sulfamethizole; in bottles of 100 and 1,000 scored tablets.

References—1. Bourque, J-P., and Gauthier, G-E.: Seven years' experience with sulfamethizole, to be published. 2. Bourque, J-P., and Joyal, J.: Canad. M.A.J. **68**:337 (Apr.) 1953. 3. Barnes, R. W.: J. Urol. **71**:655 (May) 1954. 4. Goodhope, C. D.: J. Urol. **72**:552 (Sept.) 1954. 5. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, Apr. 6-9, 1959, San Francisco, California. 6. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. **56**:66 (Mar.) 1959. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. **17**:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.

"Thiosulfil"® Forte

(BRAND OF SULFAMETHIZOLE)

Ayerst

AYERST LABORATORIES, NEW YORK 16, N.Y., MONTREAL, CANADA

New

Enhances Vitality and Still Insures Weight Loss

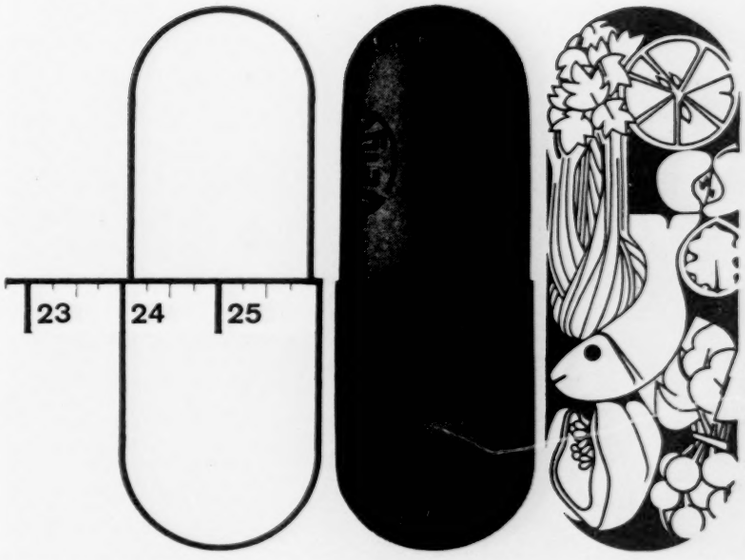
Prelu-Vite™

brand of phenmetrazine HCl with vitamins and minerals

Now, Prelu-Vite helps to fortify the patient's nutritional status and sense of well-being without jeopardizing the success of the weight-reducing program.

By improving nutritional status Prelu-Vite makes it easier for the patient to retain the initial zeal for reducing... facilitates the retention of enthusiastic cooperation in pursuing therapy to a successful conclusion.

With Prelu-Vite, as with Preludin, a weight loss 2–5 times that obtainable by dietary restriction alone, is readily achieved without the occurrence of annoying side reactions.



Geigy

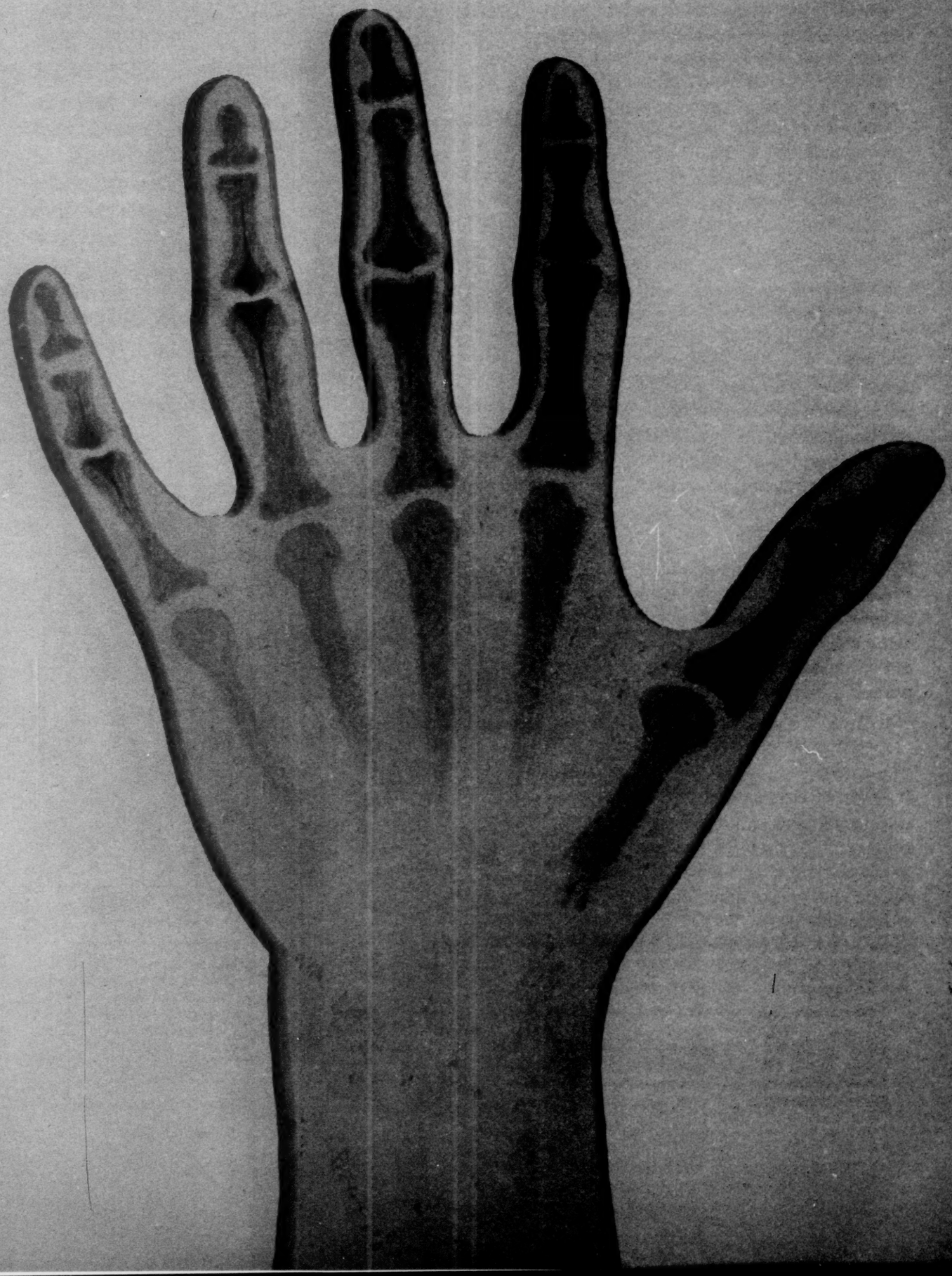
Availability:
Prelu-Vite™ – Capsules, each containing 25 mg. of Preludin (brand of phenmetrazine HCl) with vitamins A, B, C and D and 5 minerals.
Under license from C. H. Boehringer Sohn, Ingelheim.

Also available:
Preludin® Endurets®—prolonged-action tablets (75 mg.) for once daily administration; and as regular Preludin tablets (25 mg.) for b. i. d. or t. i. d. administration.

Geigy, Ardsley, New York

321-60

when the rheumatic disorder is more than salicylates alone can control...
...and the condition requires less than steroids alone



wider latitude in adjusting dosage for better tolerated therapy

ARISTOGESIC allows an exceptionally wide latitude in adjusting dosage to the lowest effective level for relief of chronic—but less severe—pain of rheumatic origin. Combining the anti-inflammatory effects of ARISTOCORT® Triamcinolone with the analgesic action of a highly potent salicylate, ARISTOGESIC permits therapy at dosages substantially lower than generally required for either agent alone. The lower dosages permit well-tolerated therapy for long periods of time and reduce the possibility of side effects.

Aristogesic®

Steroid-Analgesic Compound LEDERLE

CAPSULES

Indications: Mild to moderate cases of rheumatoid arthritis, tenosynovitis, synovitis, bursitis, spondylitis, myositis, fibrositis, neuritis, and certain muscular strains.

Dosage: Average initial dosage: 2 capsules 3 or 4 times daily. Maintenance dosage to be adjusted according to response.

Precautions: All precautions and contraindications traditional to corticosteroid therapy should be observed. The amount of drug used should be carefully adjusted to the lowest dosage which will suppress symptoms. Discontinuance of therapy must be carried out gradually after patients have been on steroids for prolonged periods.

Each ARISTOGESIC Capsule contains:

ARISTOCORT Triamcinolone	0.5 mg.
Salicylamide	325 mg.
Dried Aluminum Hydroxide Gel	75 mg.
Ascorbic Acid	20 mg.

Supply: Bottles of 100 and 1,000.

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Daricon®

Oxyphencyclimine hydrochloride

IN BRIEF

DARICON, oxyphencyclimine hydrochloride, is a long-acting highly effective anticholinergic providing potent antispasmodic and antisecretory actions. Each white, scored tablet contains 10 mg. of oxyphencyclimine hydrochloride. DARICON provides 24 hour relief from the pain and discomfort of peptic ulcers, usually with just b.i.d. dosage. A high percentage of refractory ulcer cases have responded well to DARICON.

INDICATIONS: DARICON is valuable for the adjunctive management of peptic ulcers—duodenal, gastric and marginal types; functional bowel syndrome—irritable colon, spastic colon including mucous colitis; pylorospasm, cardiospasm; chronic nonspecific ulcerative colitis; biliary tract disease, including cholecystitis and cholelithiasis; hiatus hernia accompanied by esophagitis or ulcer; gastritis, acute or hypertrophic; duodenitis; bladder spasm with or without cystitis; ureteral spasm, as with stones or pyelonephritis.

SIDE EFFECTS & PRECAUTIONS: Dryness of the mouth is the most common peripheral effect. Blurring of vision, constipation, and urinary hesitancy or retention occur infrequently. These effects may decrease or disappear as therapy continues, or can be minimized by adjustment of dosage. Caution should be exercised when using DARICON in patients with prostatic hypertrophy or glaucoma.

ADMINISTRATION & DOSAGE: The average adult dosage is 10 mg. of DARICON given twice daily—in the morning and at night before retiring. (Dosage should be adjusted in relation to therapeutic response.) As much as 50 mg. daily is acceptable to some adult patients. As little as 5 mg. daily is therapeutically effective in some adult patients.

SUPPLY: DARICON is supplied as a white scored 10 mg. tablet.

More detailed professional information available on request.

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.



It is important, in the over-all management of duodenal ulcers, that the healing process established during the waking hours continue uninterrupted during the sleeping hours.

DARICON provides naturally prolonged antispasmodic-antisecretory protection throughout the night—when ulcer control depends on continuity of anticholinergic activity. A single DARICON tablet usually permits both ulcer and patient to rest undisturbed for 8 to 12 hours. The same prolonged anticholinergic action can be provided during the daytime hours usually with just 1 DARICON tablet at breakfast.

Pfizer

Science
for the world's
well-being™

CONTINUOUS ULCER MANAGEMENT

Daricon®

Oxyphencyclimine hydrochloride

"comprehensive" multivitamins—friend or foe?



Although not itself harmful, the small amounts of folic acid in "comprehensive" multivitamins can correct significant blood disorders to confuse the diagnosis and delay the treatment of pernicious anemia victims.[1-13] Peripheral blood and bone marrow data may appear normal[1] in such patients while accompanying nerve degeneration continues. Diagnosis delayed by normal appearing indices can thus allow irreparable neurologic damage to occur before the true nature of the disease is recognized and treatment begun.[4]

To help physicians avoid this threat, Robins has formulated Adabee®, a new therapeutic multivitamin without folic acid, that is especially safe for long-term nutritional therapy in patients who require maximum support.

why no vitamin B_{12} in Adabee®?

In order to obtain therapeutic levels of specific vitamins for certain individual deficiencies, doctors must often employ a "comprehensive" multivitamin.[4,7] Many such elongated formulas include as ingredients substances which are nonessential, expensive to the patient, and irrational.[4,7,10]

On the basis that B_{12} in therapeutic vitamin mixtures has been described as needless by the A. M. A.,[2] and its unnecessary[8,10,14,15] and indiscriminate use[1] has been criticized by astute hematologists,[7] internists,[10] pathologists,[12,13] and nutritional workers,[2] this member of the B-complex has also been omitted from Adabee.

In a rational formula,[2,4,16,17] the need for hormones, enzymes, amino acids, or yeast is not supported. And since these superfluous substances might encumber the desired response to concurrently administered drugs, they are not found in the Adabee formulas.

Each yellow, capsule-shaped Adabee® tablet contains:

Vitamin A	25,000 USP units
Vitamin D	1,000 USP units
Thiamine mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Nicotinamide (niacinamide)	50 mg.
Calcium pantothenate	10 mg.
Ascorbic acid (vitamin C)	250 mg.

Each green, capsule-shaped Adabee®-M tablet contains Adabee, plus nine minerals:

Iron	15.0 mg.
Iodine	0.15 mg.
Copper	1.0 mg.
Manganese	1.0 mg.
Magnesium	6.0 mg.
Zinc	1.5 mg.
Potassium	5.0 mg.
Calcium	103.0 mg.
Phosphorus	80.0 mg.

references:

1. Ellison, A. B. C., J.A.M.A., 173:240, 1960. 2. White, P. L., Sec'y, A.M.A. Council on Foods and Nutrition, J.A.M.A., 169:41, 1959. 3. New Eng. J. M., Vol. 259, No. 25, Dec. 18, 1958, p. 1231. 4. Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 2nd ed., New York, Macmillan, 1955, pp. 1709-10, 1489-91. 5. *Federal Register*, Vol. 25, No. 136, July 14, 1960, p. 6633. 6. Conley, C. L., and Krevans, J. R., New Eng. J. M., 245:529-31, 1951. 7. Wintrobe, M. M., *Clinical Hematology*, 3rd ed., Phila., Lea & Febiger, 1952, pp. 398-400. 8. Frohlich, E. D., New Eng. J. M., 259:1221, 1958. 9. Vilter, R. W., *Modern Medicine*, 28:15, p. 90, Aug. 1960. 10. Bean, W. B., *Drugs of Choice: 1960-61*, W. Modell, ed., St. Louis, C. V. Mosby Co., 1960, pp. 115-16. 11. Crosby, W. H., Col., M.C., U.S.A., *Military Medicine*, 125:233, April, 1960. 12. Harris, C. E. C., Conn. State Med. J., pp. 543-45, July 1958. 13. Todd, Sanford, and Wells, *Clinical Diagnosis By Laboratory Methods*, 12th ed., W. B. Saunders, Phila., 1954, pp. 306-7. 14. Goldsmith, G. A., Am. J. of M., 25:680, Nov. 1958. 15. Darby, W. J., Am. J. of M., 25:726, Nov. 1958. 16. *GP*, Vol. XVIII, No. 2, p. 119, Aug. 1958. 17. J.A.M.A., Vol. 173, No. 16, pp. 1831-32, 1960.

the multivitamin without folic acid . . . or B_{12}

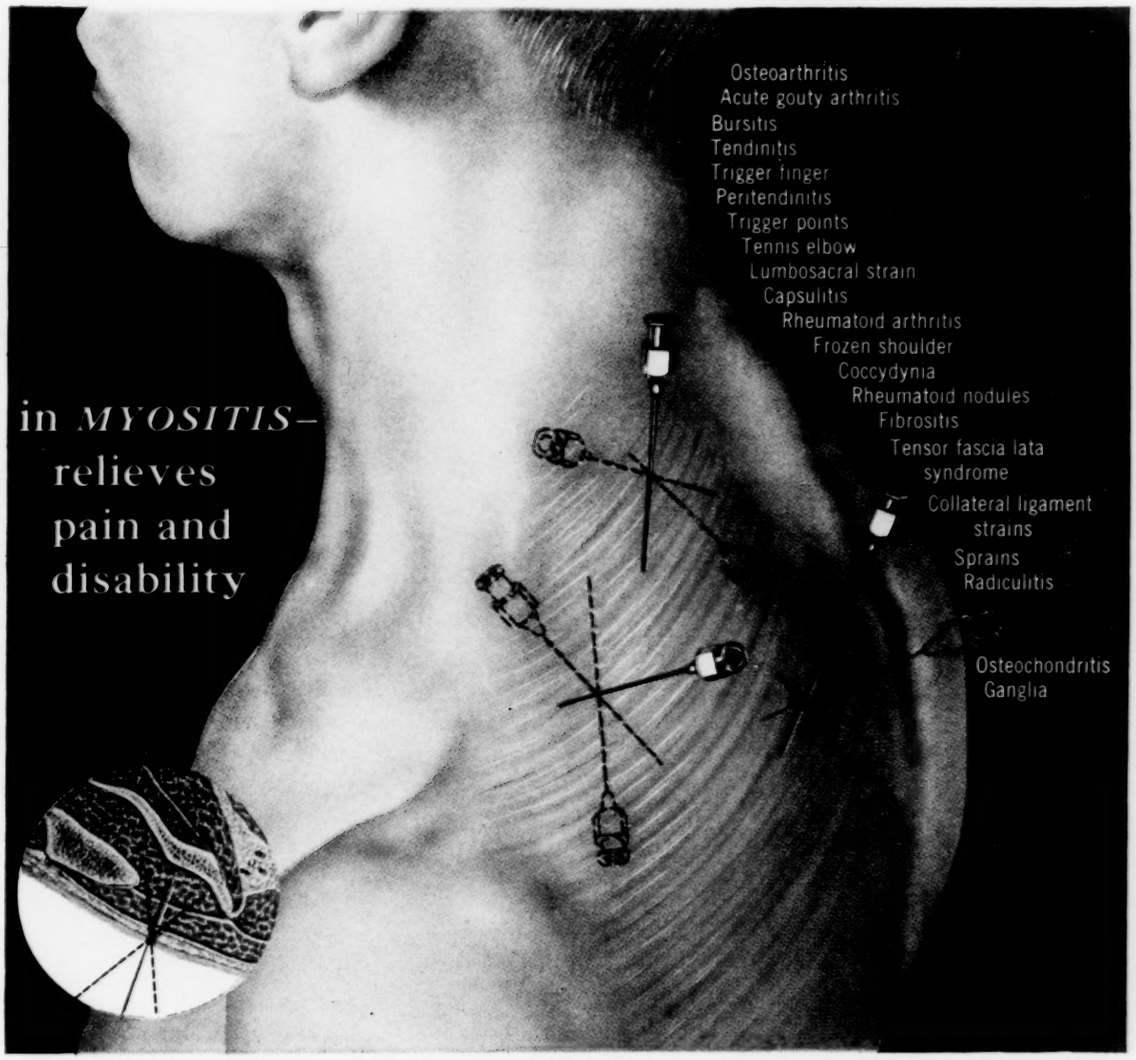
new! Adabee®

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Richmond 20, Va.

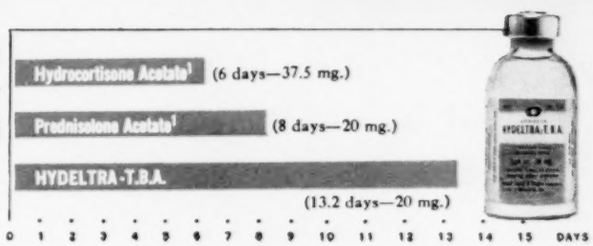
HYDELTRA® -T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory effect lasts longer than that provided by any other steroid ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

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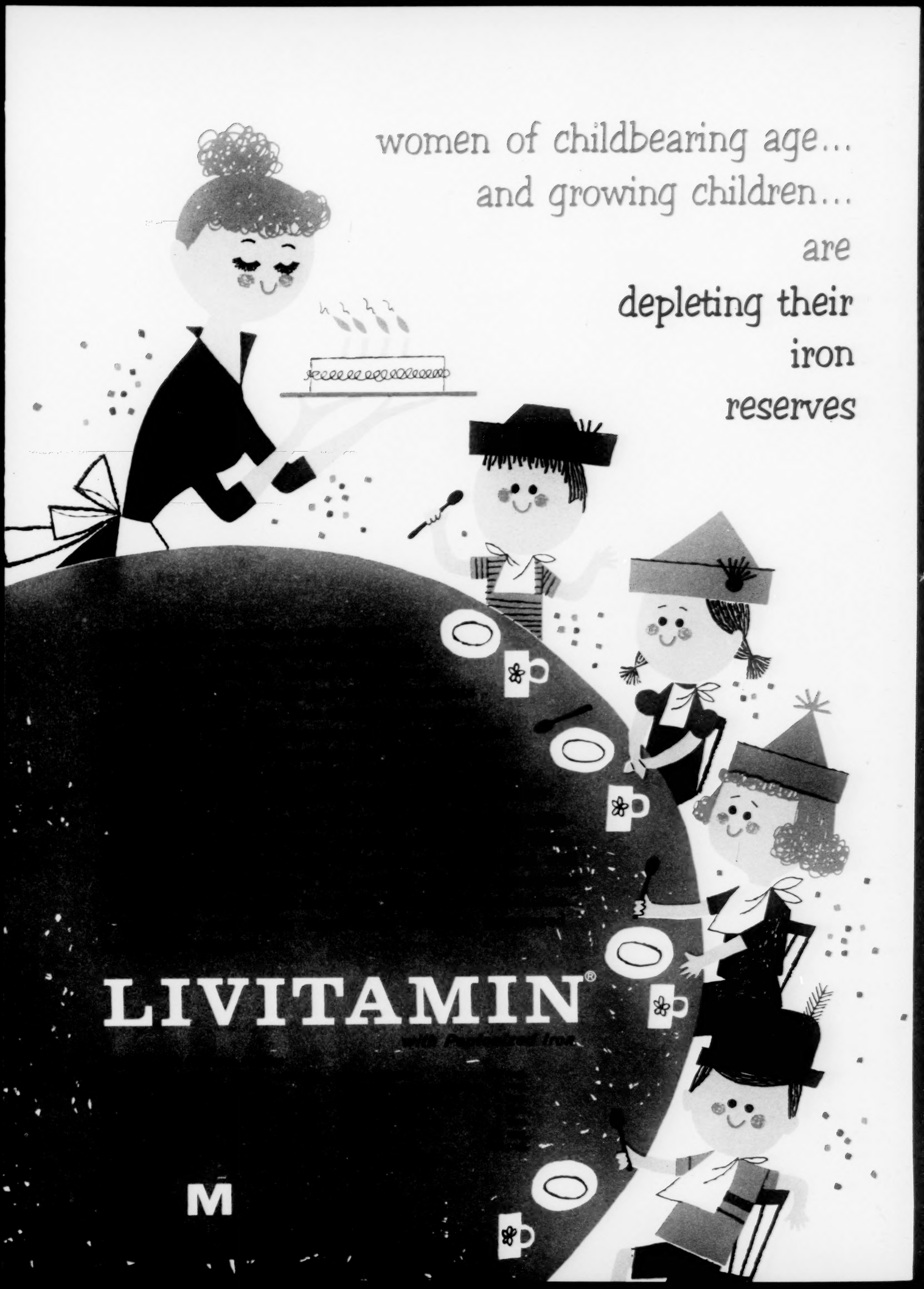
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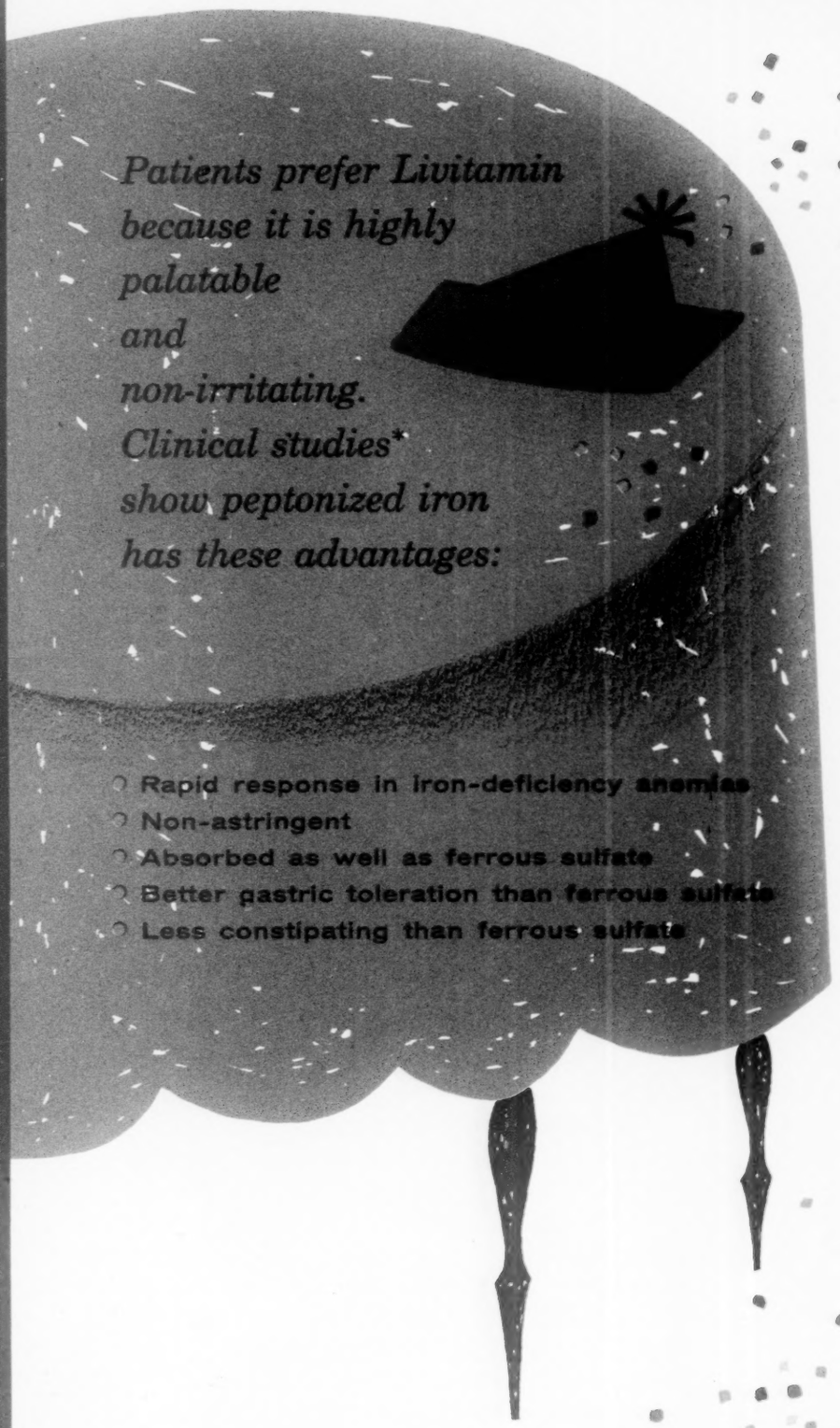
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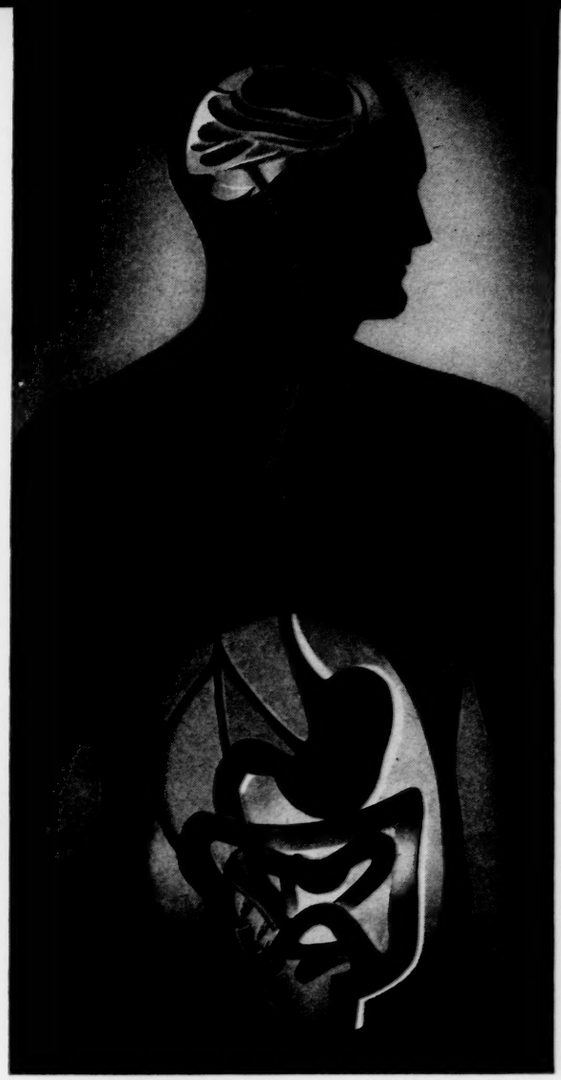
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Bibliography: 1. Ostrowski, J. P.: Orthopedics **2**:7 (Jan.) 1960. **2.** Kestler, O. C.: J. A. M. A. **171**:2039 (April 30) 1960. **3.** Frankel, K.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959.

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References: 1. Steigmann, F., **et al.**: Am. J. Gastroenterol. **33**:109 (Jan.) 1960. 2. Hock, C. W.: to be published. 3. Leming, B. H., Jr.: Clin. Med. **6**:423 (Mar.) 1959. 4. Data in Roerig Medical Department Files.

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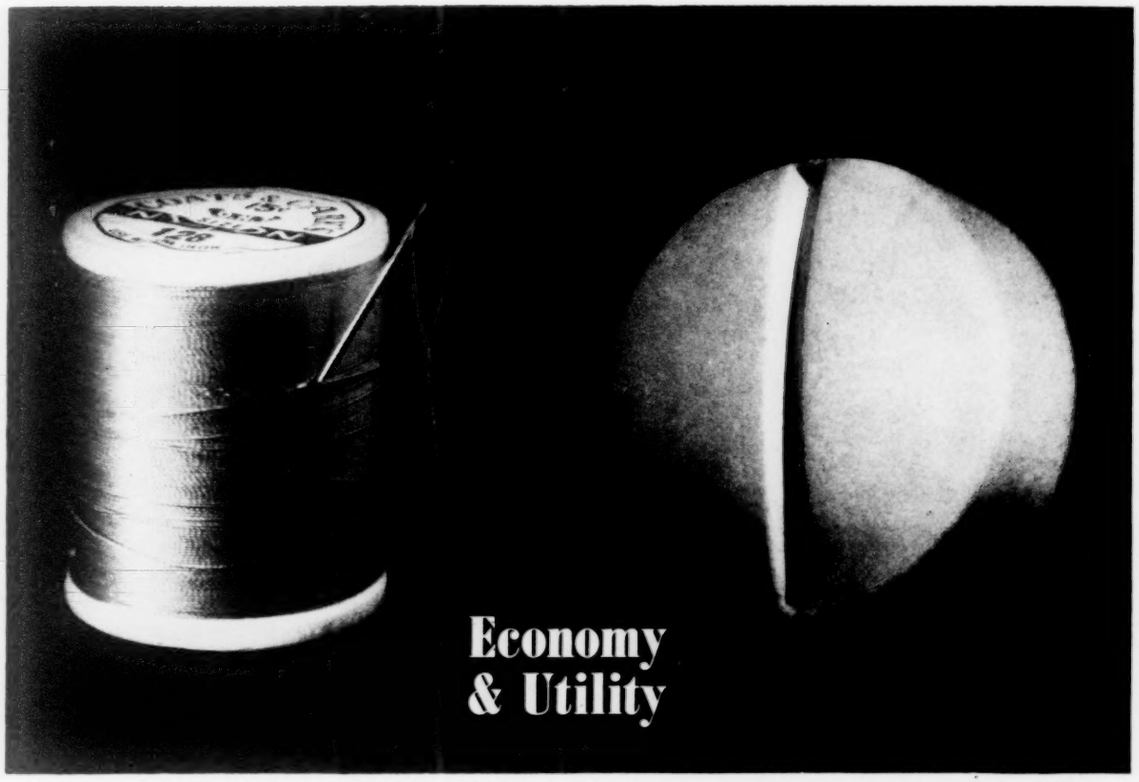
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1. Kasich, A. M., Relief of Nocturnal Pain in Duodenal Ulcer, Am. J. Gastroenterol., 33:66, January, 1960. **2.** Kasich, A. M. and Fein, R. D., Hexocyclium Methosulfate in Active Duodenal Ulcer: Evaluation of a New Anticholinergic Drug in Conventional and Long-Acting Forms, Especially its Effect on Gastric pH as studied in 48-hour Analysis, Am. J. Digest. Dis., 3:12, January, 1958. **3.** Kasich, A. M., Hexocyclium Methosulfate, a New Anticholinergic Drug in Conventional and Long-Acting Forms: Its Effect on Gastric Secretion, Schweiz. Ztschr. allg. Path., 21:354, 1958.

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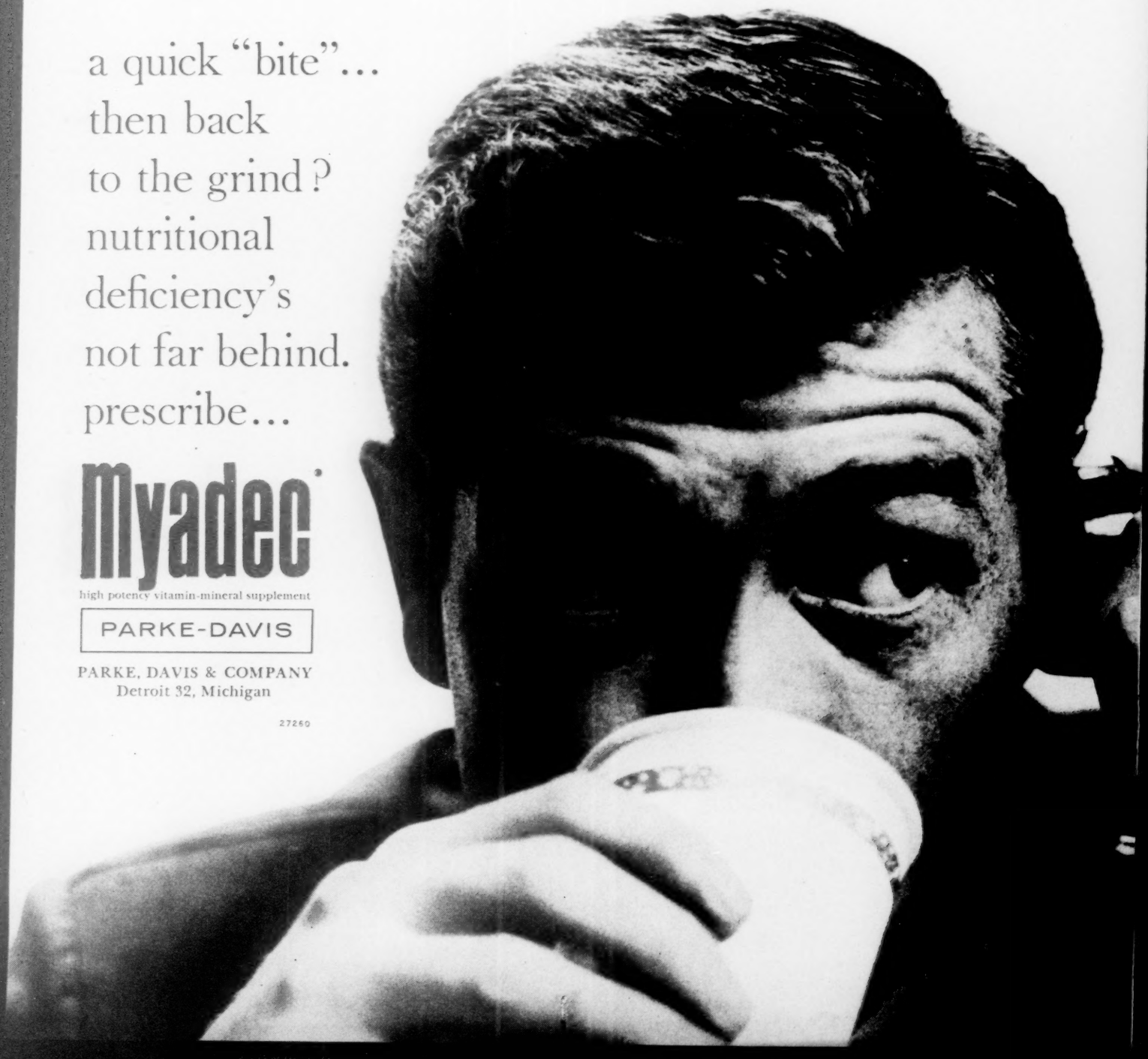
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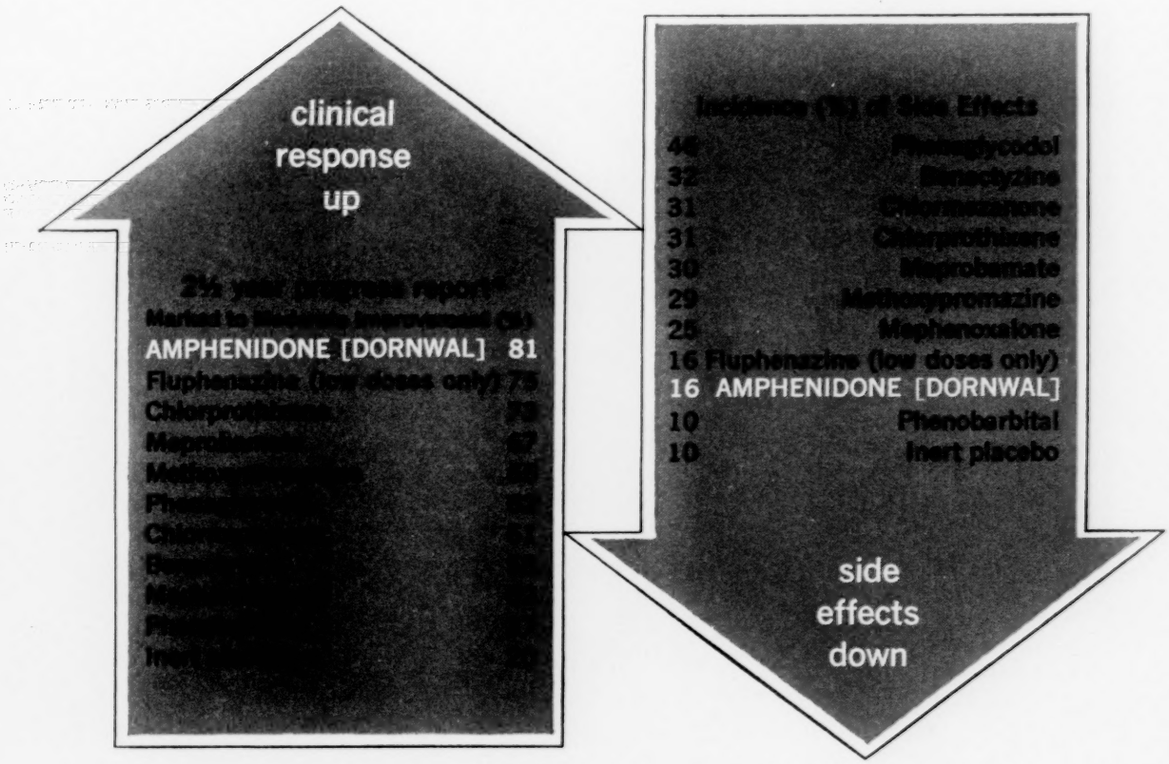


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*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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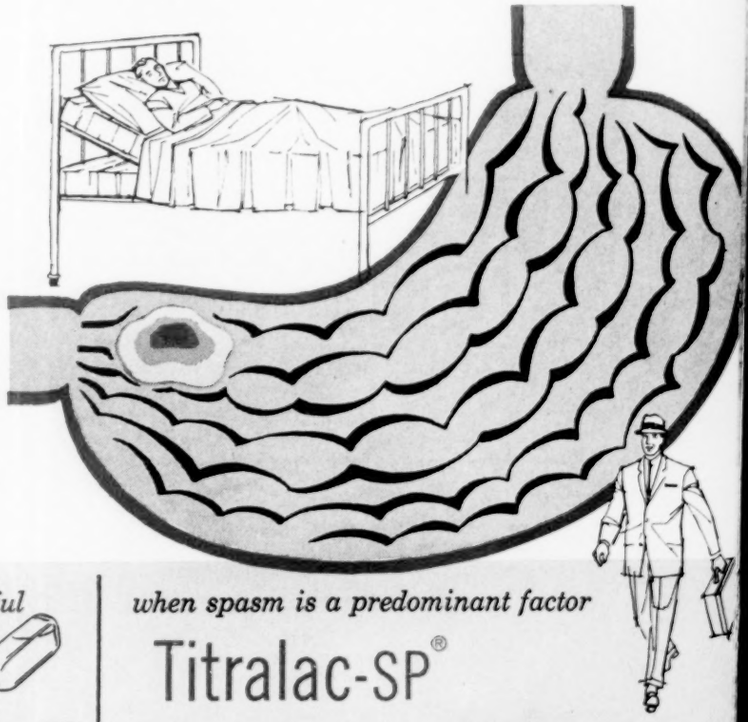
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1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

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11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. **12.** Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. **13.** Pollak, M.: Practitioner 184:231, Feb. 1960. **14.** Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. **15.** Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. **16.** Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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HOW SUPPLIED: *Vistaril Parenteral Solution*—10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. *Vistaril Capsules* (as the pamoate)—25, 50, and 100 mg. *Oral Suspension* (as the pamoate)—25 mg. per 5 cc. teaspoonful.

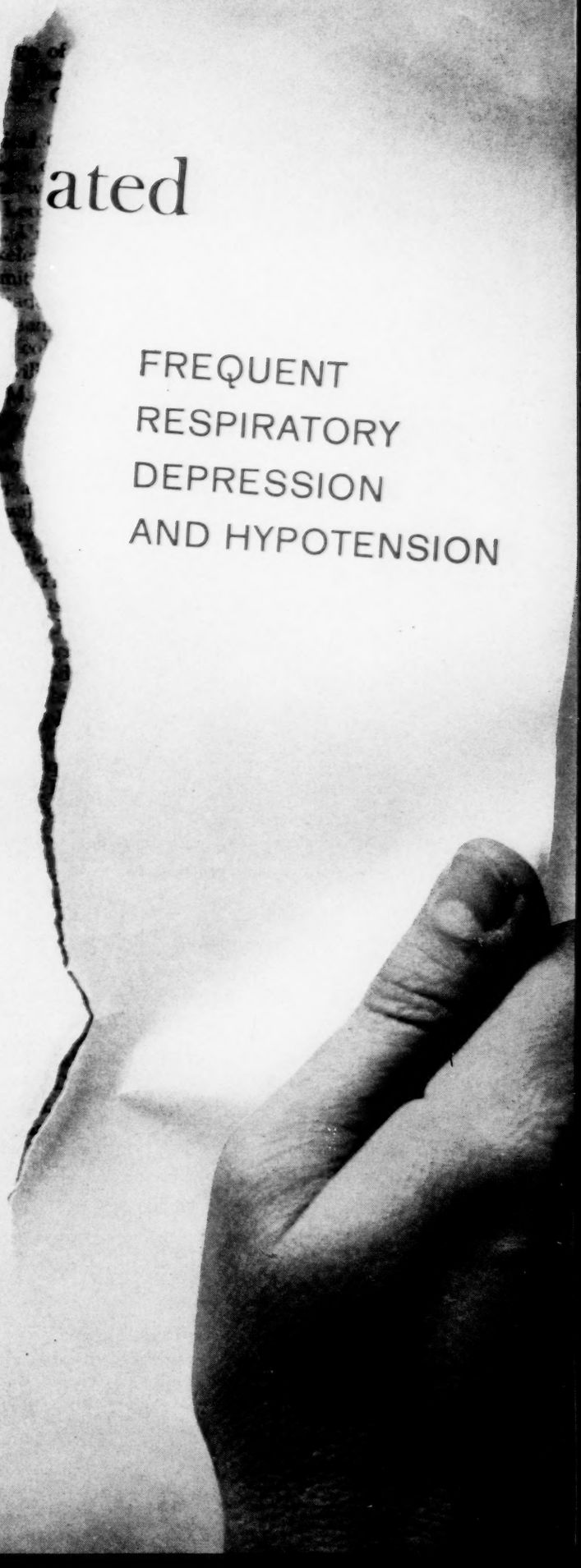
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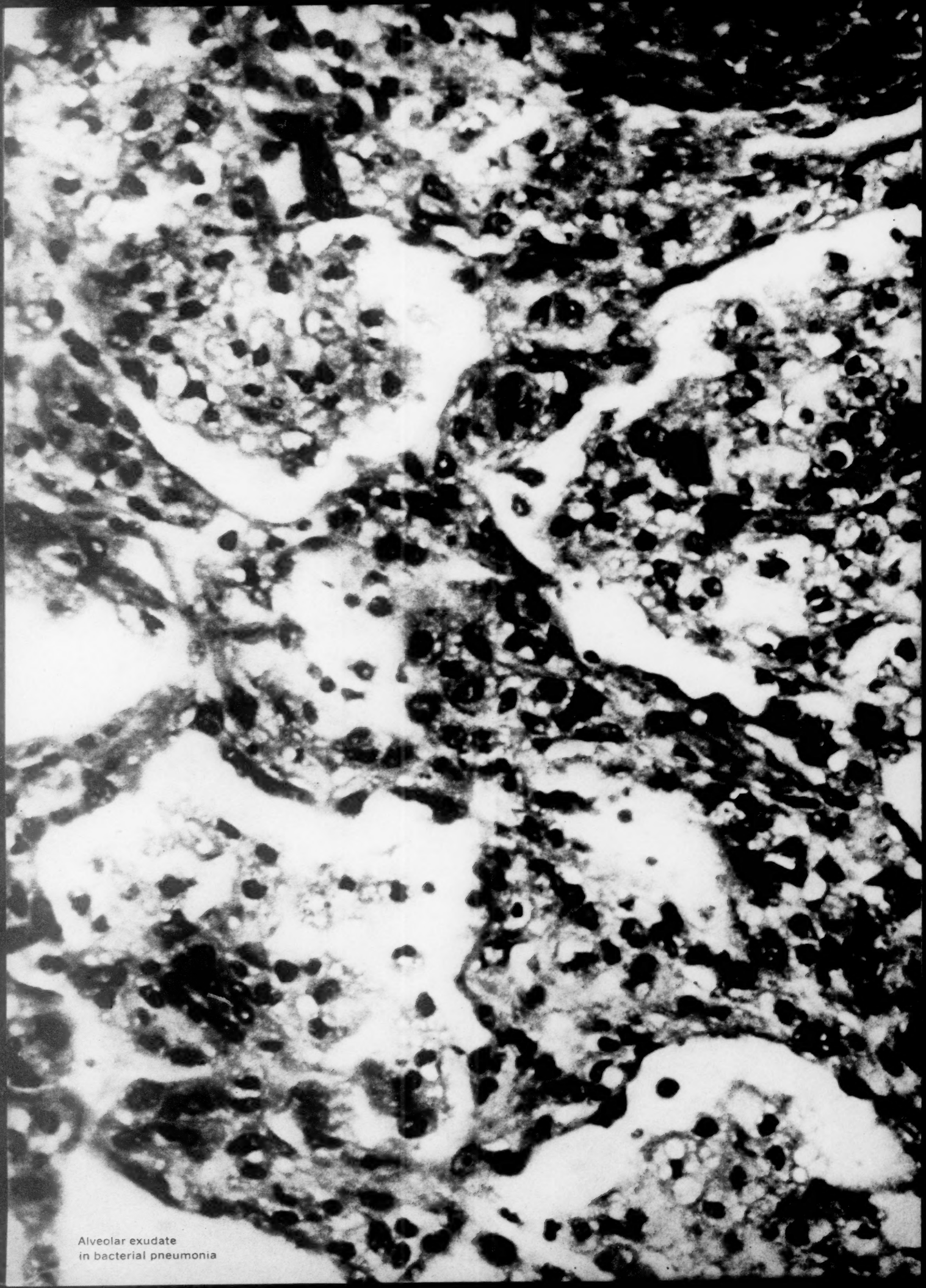
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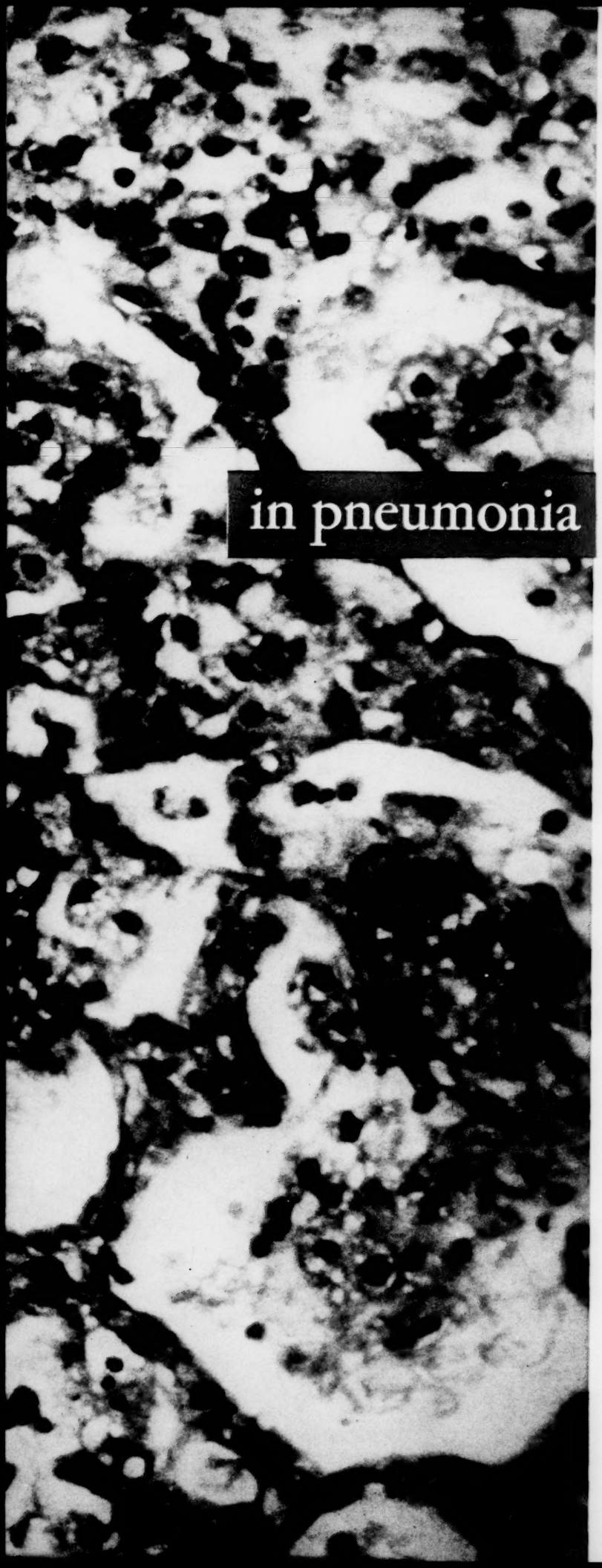
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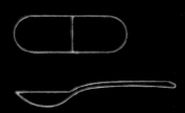
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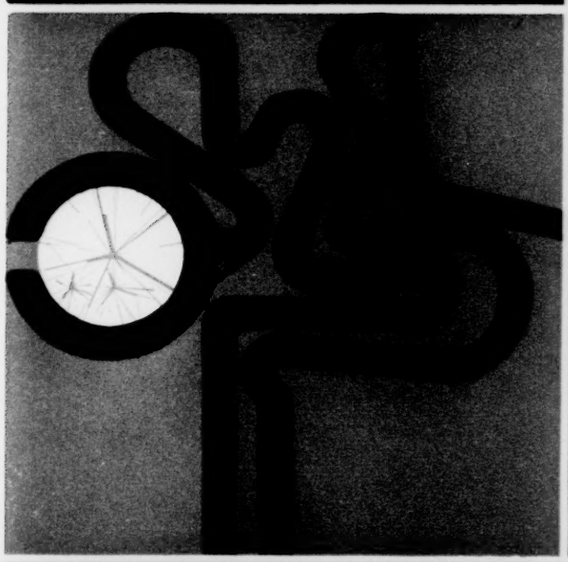
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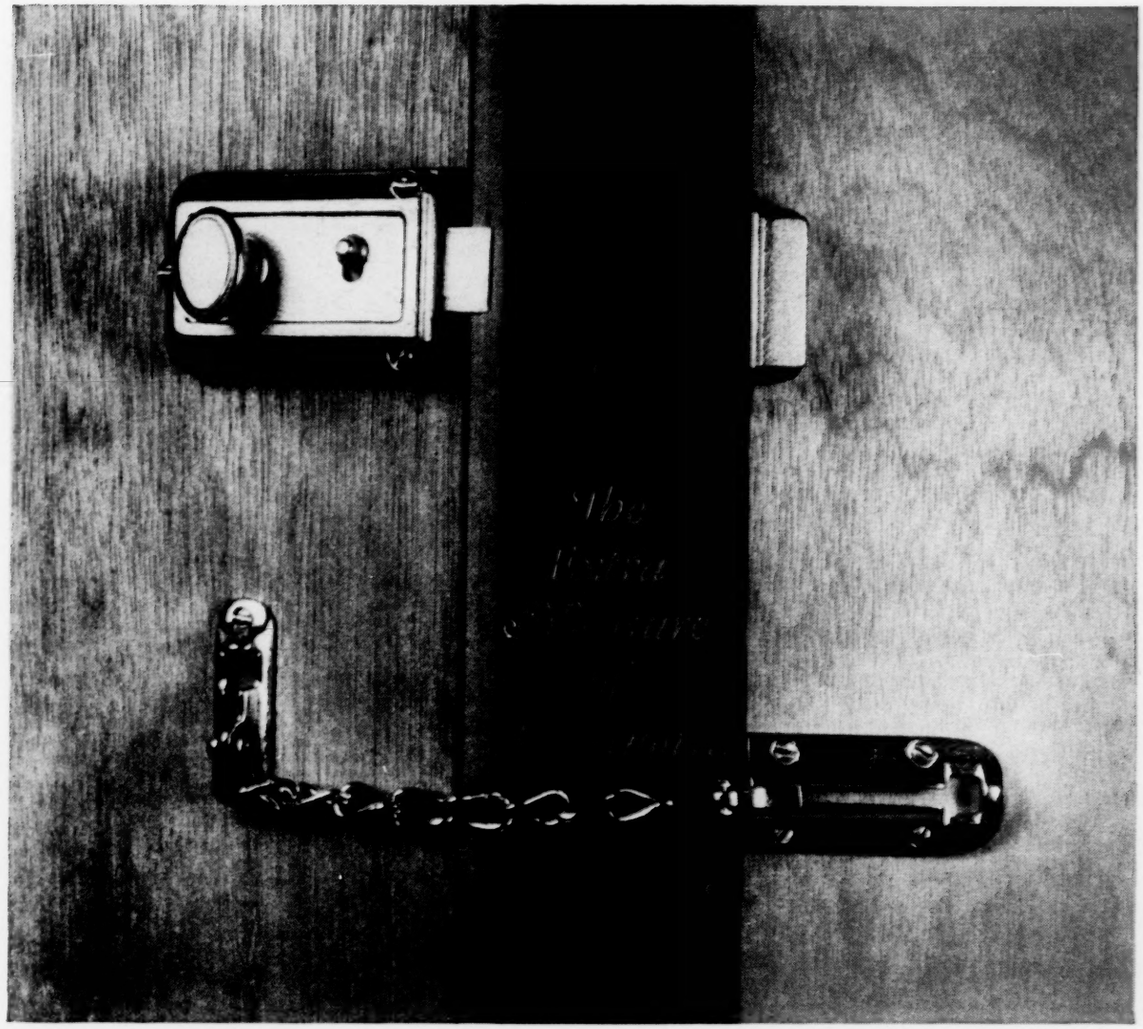
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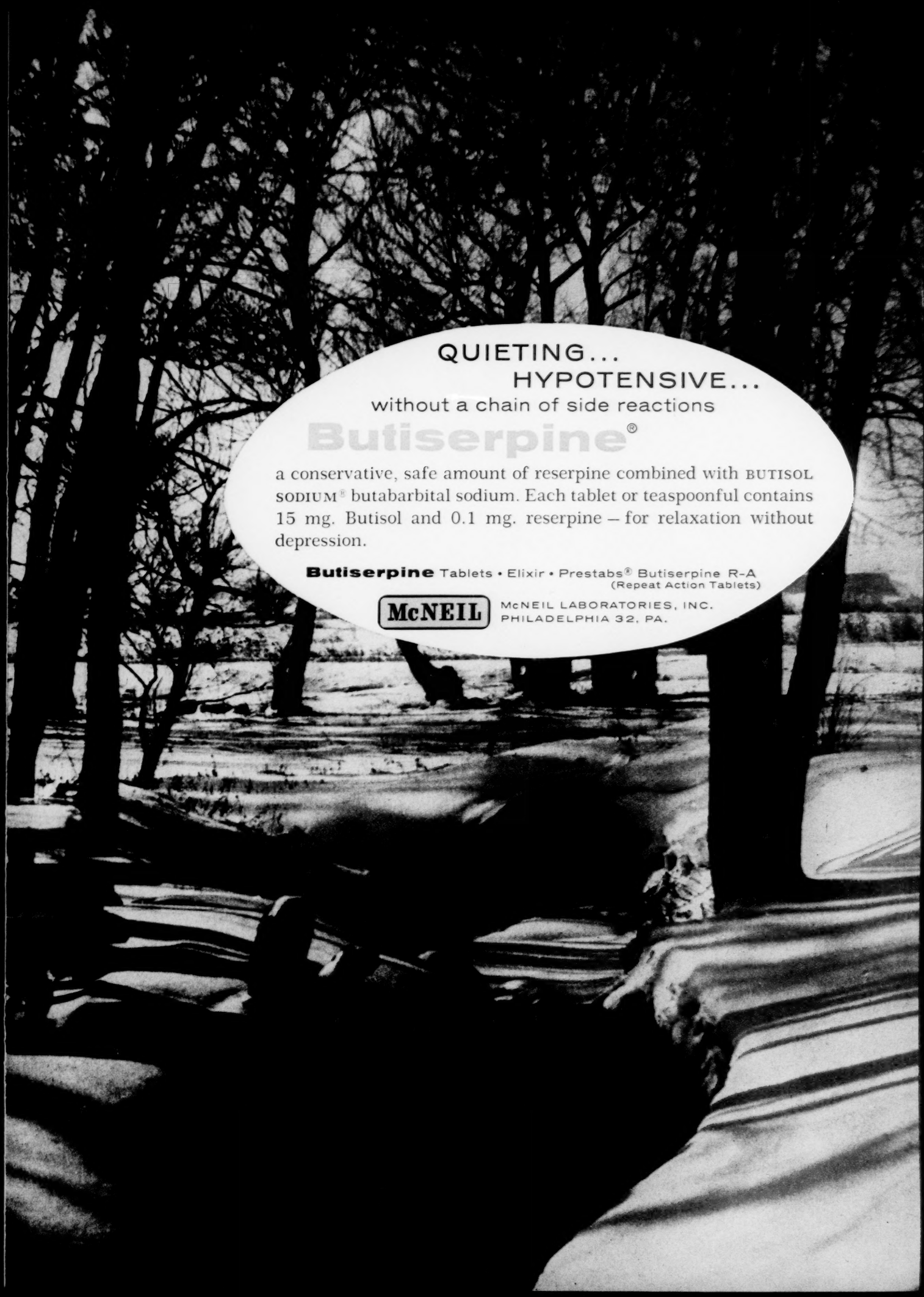
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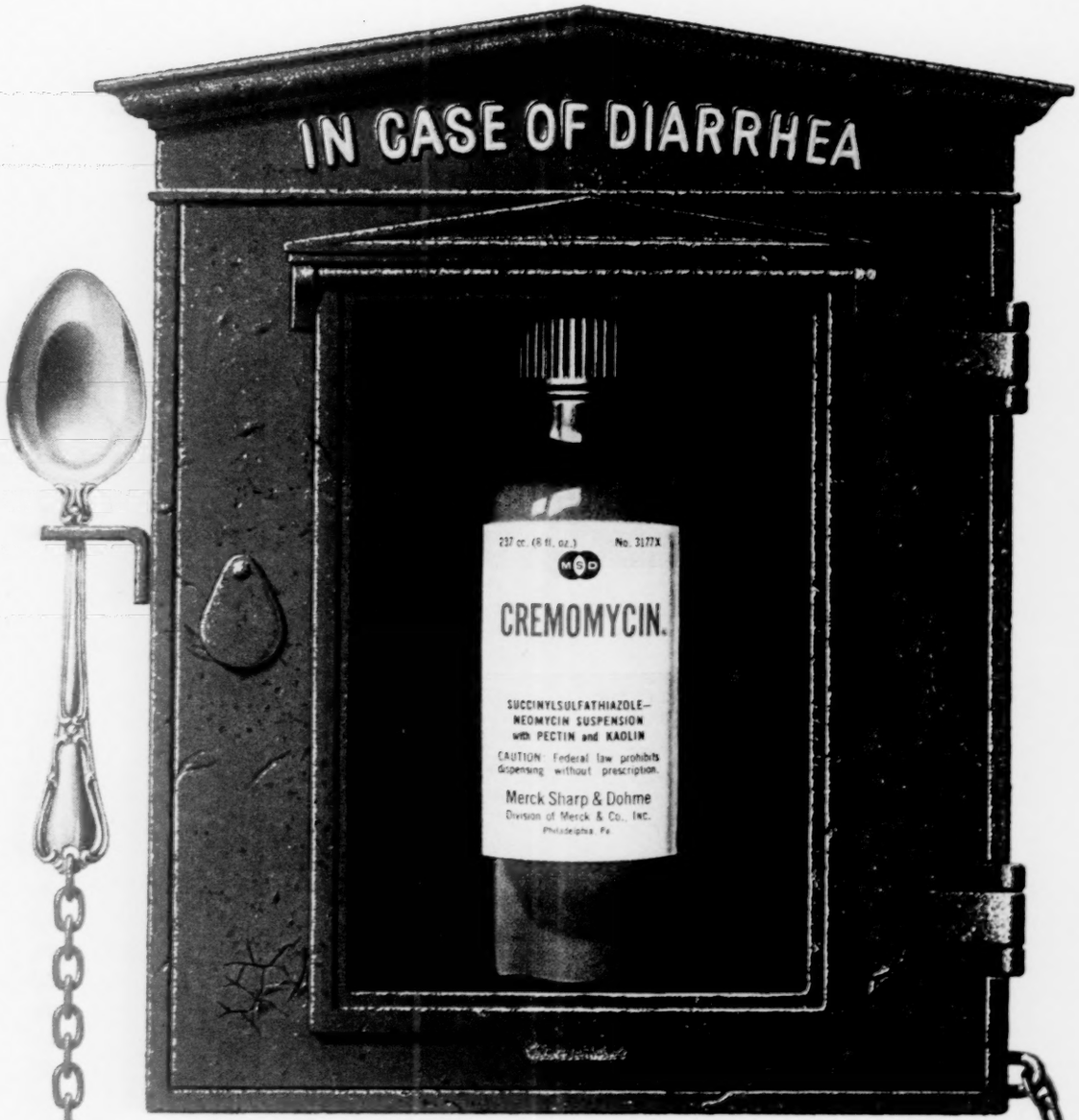
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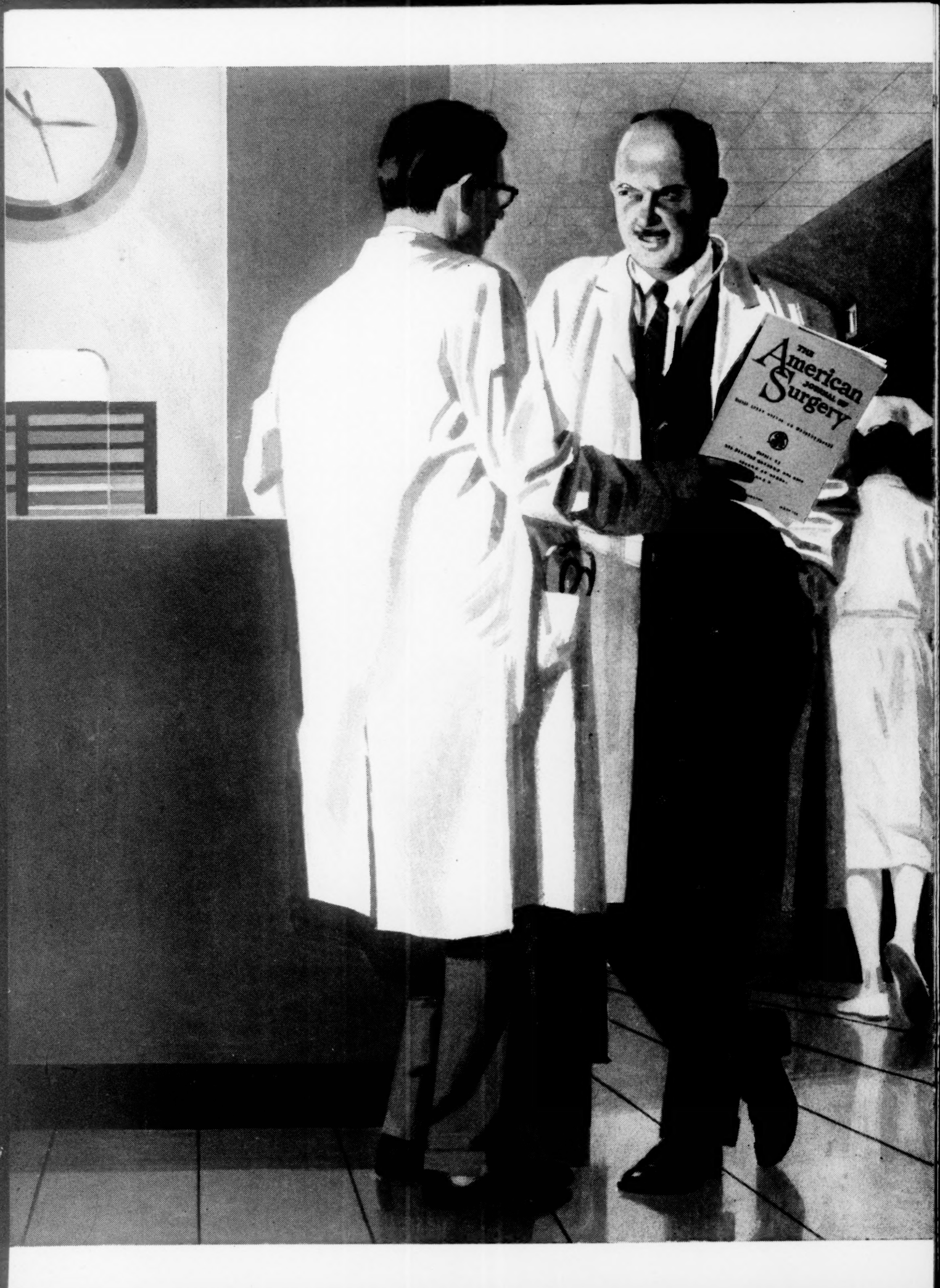
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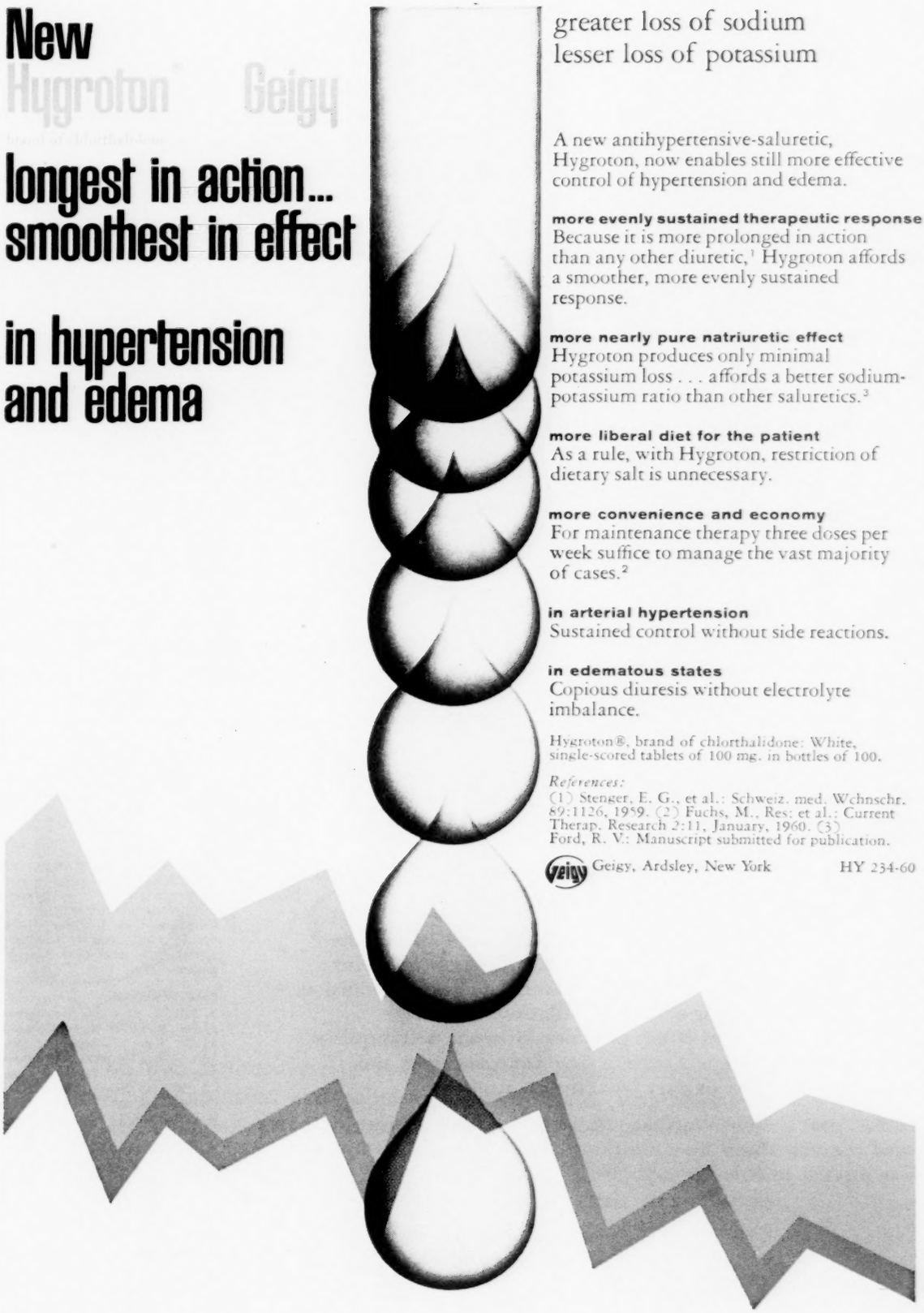
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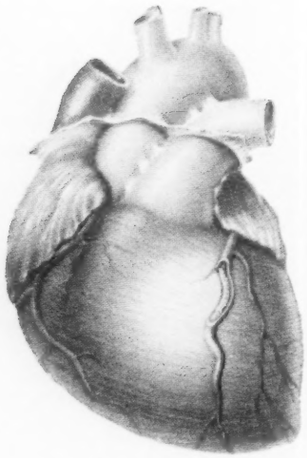
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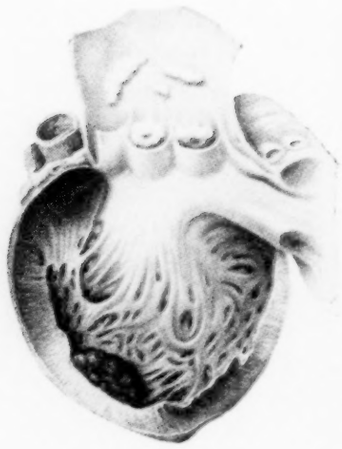
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REFERENCES

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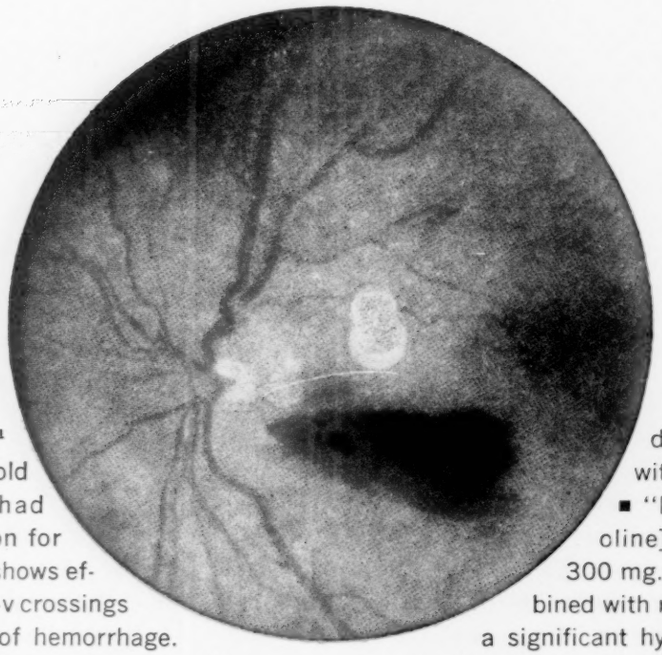
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